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SUICIDAL BEHAVIOUR IN THREE HIGH-RISK POPULATIONS

EPIDEMIOLOGICAL AND CLINICAL COHORT STUDIES

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Karolinska Institutet

Stockholm 2015

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Published by Karolinska Institutet.
Front cover *Den sjunde kontinenten* by Maja K Zetterberg, 2015
Printed by E-Print AB, 2015

ISBN 978-91-7676-105-2

SUICIDAL BEHAVIOUR IN THREE HIGH-RISK POPULATIONS – EPIDEMIOLOGICAL AND CLINICAL COHORT STUDIES

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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Dedicated to the quite fantastic Charlotte, my extraordinary sister Frida, and my always supportive and loving parents Karin and Birger. My gratitude cannot be expressed in words.

ABSTRACT

Aims

The subject of this thesis is risk factors for suicidal behaviour in three high-risk populations; bipolar patients, released prisoners and suicide attempters, to provide knowledge for improvement of strategies for preventing suicide. In study I, we investigated factors related to bipolar disorder and the risk for suicidal behaviour. Study II analysed the role of psychiatric risk factors in released prisoners. The objective in study III was to evaluate the ability of the Karolinska Interpersonal Violence Scale (KIVS) to predict repeated suicidal behaviour in a cohort of suicide attempters within six months.

Methods

All three studies are cohort studies by design. Study I is based on 6 068 bipolar patients from the quality register BipoläR followed-up between 2005 and 2012. Studied outcome is suicidal behaviour during follow-up. Studied risk factors include characteristics of the bipolar disorder and psychiatric comorbidity. Study II is based on 26 985 prisoners who were released 38 995 times during 2005–2009. Data for this study comes from population-based registers and studied outcome is completed suicide. Study III is based on a clinical sample of 355 suicide attempters who have been interviewed with the KIVS. Studied outcome is repeated suicidal behaviour within six month.

Results

The most important risk factors for suicidal behaviour in study I were previous suicide attempts (OR = 3.9 for men, 4.2 for women), recent affective episodes (OR = 3.6 for men, 2.8 for women) and recent psychiatric inpatient care (OR = 3.6 for men, OR = 2.7 for women). Risk was also elevated by co-morbidity with personality disorder for women and substance use disorder for men. In study II a total of 127 suicides occurred among the released prisoners. The incidence was 18 times higher compared with non-convicted general population controls. Previous suicide attempt (HR = 2.5), substance use disorder (HR = 2.1), and being born in Sweden versus abroad (HR = 2.1) were independent risk factors for suicide after release. Affective disorders were less prevalent in ex-prisoner suicides compared with suicides in the non-convicted control group. In study III repeated suicidal behaviour was observed in 78 persons (22%) within six months. To have a KIVS total-score of 6 and above was associated with an increased risk of repeated suicidal behaviour (OR = 1.8) and predicted repetition with a sensitivity of 62% and a specificity of 53%.

Conclusions

The principal clinical implications are that 1) a clinician should be observant of the risk of suicidal behaviour in bipolar patients who display depressive features and a more unstable disorder, 2) released prisoners constitute a high risk population for suicide and information about previous suicidal behaviour and substance use disorder is important for the assessment of risk in this population, 3) information about interpersonal violence may enhance the prediction of short-term risk for repeated suicidal behaviour.

LIST OF SCIENTIFIC PAPERS

I. Dag Tidemalm, AXEL HAGLUND, Alina Karanti, Mikael Landén, Bo Runeson. Attempted suicide in bipolar disorder: risk factors in a cohort of 6086 patients. PLoS One. 2014 Apr 4;9(4):e94097

II. AXEL HAGLUND, Dag Tidemalm, Jussi Jokinen, Niklas Långström, Paul Lichtenstein, Seena Fazel, Bo Runeson. Suicide after release from prison: a population-based cohort study from Sweden. Journal of Clinical Psychiatry. 2014 Oct;75(10):1047-53

III. AXEL HAGLUND, Åsa Lindh, Henrik Lysell, Ellinor Salander Renberg, Jussi Jokinen, Margda Wærn, Bo Runeson. Interpersonal violence and the prediction of short-term risk of repeated suicide attempt. Manuscript.

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention Deficit Hyperactivity Disorder
AUC	Area Under the Curve
CI	Confidence Interval
DSM-IV	The Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders
ECG	Electro-cardiogram
FDA	Food and Drug Administration
HR	Hazard Ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
KI	Karolinska Institutet
KIVS	Karolinska Interpersonal Violence Scale
MEB	Department of Medical Epidemiology and Biostatistics at KI
NIMH	National Institute of Mental Health
NOS	Not Otherwise Specified
NSSI	Non-Suicidal Self-Injury
OR	Odds Ratio
ROC	Receiver Operating Characteristic
RR	Relative Risk
SADB	Schizoaffective Disorder Bipolar type
SD	Standard Deviation
SMR	Standardised Mortality Ratio
5-HIAA	5-Hydroxy Indole Acetic Acid

1 BACKGROUND

1.1 INTRODUCING THE PROBLEM

During my own cognitive development, around six years of age, I remember that I started to ask myself: *How should I be? How should I think and behave? What should I do?* The questions were not about overarching goals in life but very concrete and associated with specific situations, for instance when lying in bed, looking up at the ceiling, thinking about what to do on a Saturday morning. Should I get up now or sleep some more? Or out on the football field; precisely where should I be and how should I move around the pitch? Or, when being told specifically what to do, should I obey? No one never really told me how to make decisions in life, not in perfect detail. And if I did something, exactly which facial expression should I have? What should be the purpose of my actions? Of course, my parents and others told me how to behave and sometimes I got more elaborate directions too, but exactly how I should be was never explained to me. Life did not come with instructions. I eventually found that I was left to figure these things out for myself. I learned to improvise, thinking that this is what everybody else does all the time; and by doing so silently answering the profound question *How should I be?* Years later, the concept of suicide was introduced to me by other people talking about it. I have no recollection of having any spontaneous thoughts about suicide before. When I started working in a psychiatric ward specialised in suicidal patients during the summer of 1997, I found that many people struggle with an even more fundamental question, preceding the familiar questions I previously had encountered: *Should I be at all*?

There is but one truly serious philosophical problem, and that is suicide[1].

I believe that Albert Camus' introduction in "La mythe de Sisyphe" captures something fundamental about the human condition. Human beings seem to be the only species capable of reflecting on the nature of their own existence, and with a free will to shape their own future. At some point in the evolution of Homo sapiens, when this developmental step occurred, suicide surfaced as a possibility. And so it has continued to be, independent of whether a person articulates the question or not. For some people the question never emerges consciously and is thus unknowingly answered, and for some it is always more or less present, demanding an answer. The question is easy to answer for many and extremely difficult for others, and the answer can fluctuate substantially during a person's life span. The question may serve as a fertile starting point in the search of what makes life meaningful, but can also lead to an agonising psychological short-circuit when living seems impossible and thoughts translate into suicidal behaviour. The universal humanity at the core of this question is also what makes suicidal behaviour so harrowing, forcing fellow human beings to halt and re-evaluate their own answers.

1.1.1 Historical perspective

The act of taking one's own life has been looked upon in different ways historically. Greeks and Romans saw it as an honourable way of death, if the person was not a slave and if the circumstances were right. The early Christian church decided instead that suicide was to be considered a sin, a standpoint that for centuries shaped the general attitude in Christian societies. In the western world, attitudes towards suicide began to change during the Renaissance and the Enlightenment, and suicidal behaviour was decriminalised in most European countries by the end of the nineteenth century[2]. Camus' existentialist perspective on suicide exemplifies an individualistic stance on the right to commit suicide that has become more established during the 20th century. Investigations of communication about suicide on the Internet in the early 2000s, show that permissive attitudes are widespread[3]. In Japan, the ancient phenomenon *Seppuku*, an example of a traditional and culturally accepted ritual suicide, is still not an uncommon cause of death. Suicide bombing is an example of suicidal behaviour that is accepted and even encouraged, in certain extreme interpretations of Islam. The legalisation of assisted suicide, in for instance Switzerland, also indicates a deviation from the traditional standpoint that suicide is always ethically indefensible. However, in some other parts of the world, for instance in Ghana, Singapore and India, suicide is still considered a criminal act and suicide attempters can even be imprisoned[4].

1.1.2 Current situation

Today, at least one person commits suicide world-wide every minute[5]. It equals more than 800 000 certain suicides per year and corresponds to an age-standardised suicide rate of eleven deaths per 100 000 persons annually. Of all causes of death, suicide accounts for around 1.4% and was the 15th leading cause of death globally in 2012. Among 15-29-year-olds, suicide is the second leading cause of death. In Sweden, it is the most common cause of death among men between 15 and 44 years and accounts for 30% of all deaths in this group. Among women in Sweden, it is the most common cause of death in the age group 15-24 years[6]. Almost all suicides have a profound negative effect emotionally, socially and economically on family, friends and surrounding society. The mean societal cost for one suicide was estimated to exceed $1 million in the US in 2010[7] and even higher costs have been reported in Sweden[8].

The majority of suicide attempts do not lead to immediate contact with the healthcare system. Hence, it is difficult to estimate the prevalence with absolute certainty. On average, five suicide attempters are treated in hospital per completed suicide in Sweden[9]. However, population surveys indicate that for every suicide, approximately 20 persons make attempts, but survive[5]. The high ratio between attempts and completed suicides reflects the large amount of ambivalence that characterises people who consider suicide. Nonfatal suicide attempts represent a big public health problem in their own right, not only because of the immediate medical consequences and the fact that they sometimes precede completed suicide, but also because of the mental suffering signalled by the behaviour. Thus, prevention of all kinds of suicidal behaviour is a prioritised task in many western countries[10].

1.2 DEFINITIONS OF SUICIDAL BEHAVIOUR

The term suicidal behaviour includes completed suicide and suicide attempts, but sometimes also suicidal thoughts, suicide threats and plans. In this thesis, however, the term suicidal behaviour is consistently restricted for suicide and suicide attempts. The nomenclature used in suicide research has unfortunately been lacking a general consensus. Terms like suicidality, parasuicide and self-harm have been used inconsistently and with different meanings. In 1996, O'Carroll and co-workers[11] suggested a standardisation of the taxonomy to improve clarity, and Silverman and co-workers[12,13] made an ambitious revision in 2007. However, still today, no single detailed definition has been universally endorsed.

WHO shortly defines suicide as "the act of deliberately killing oneself"[5]. WHO's definition and many other relevant definitions include at least two necessary logical steps:

> 1) a deliberate act with the purpose to harm oneself (an observable behaviour, often labelled as deliberate self-harm), and
> 2) an intention that this act should result in his or her death (an intrinsic property within the subject).

The end result of the behaviour can be fatal and is thus called a suicide, or nonfatal and is thus called a suicide attempt. However, suicide intent, like all intrinsic states, can be difficult to assess by an observer, as it may be associated with both ambivalence and secrecy. For this reason, some suicide researchers avoid the term suicide attempt and focus instead on the observable behaviour, using the term deliberate self-harm, and leaving the question of suicidal intention unanswered. Hence, deliberate self-harm usually also includes non-suicidal self-injury (NSSI), which is a behaviour often related to coping with anguish and may have little to do with an intention to die. Also, the ICD-codes corresponding to suicide and suicide attempts include death from deliberate self-harm both with and without intention to die and nonfatal deliberate self-harm with or without intention to die.

It could be argued that there are inherent problems with studying completed suicide and suicide attempt together. The heterogeneity of behaviours included in the term suicidal behaviour used in this thesis, is undeniable. Arguably, there are many differences between an impulsive nonfatal attempt by intoxication with a small dose of sleeping pills in front of a spouse, and a carefully planned suicide by hanging in a secluded spot. Still, only coincidence and chance may separate nonfatal from fatal suicidal acts. In other words, the behaviour may be the same but the outcome differs due to circumstances. This motivates the study of not only fatal suicidal behaviour.

As a consequence of using an ICD-based population register, study II in this thesis relies on the definition of suicidal behaviour that includes NSSI. Study I and III utilise the stricter definition demanding a reported intention to die that motivates the behaviour. In these studies, information about intention was possible to obtain since interviews were used to evaluate the included patients.

1.3 EPIDEMIOLOGY OF SUICIDAL BEHAVIOUR

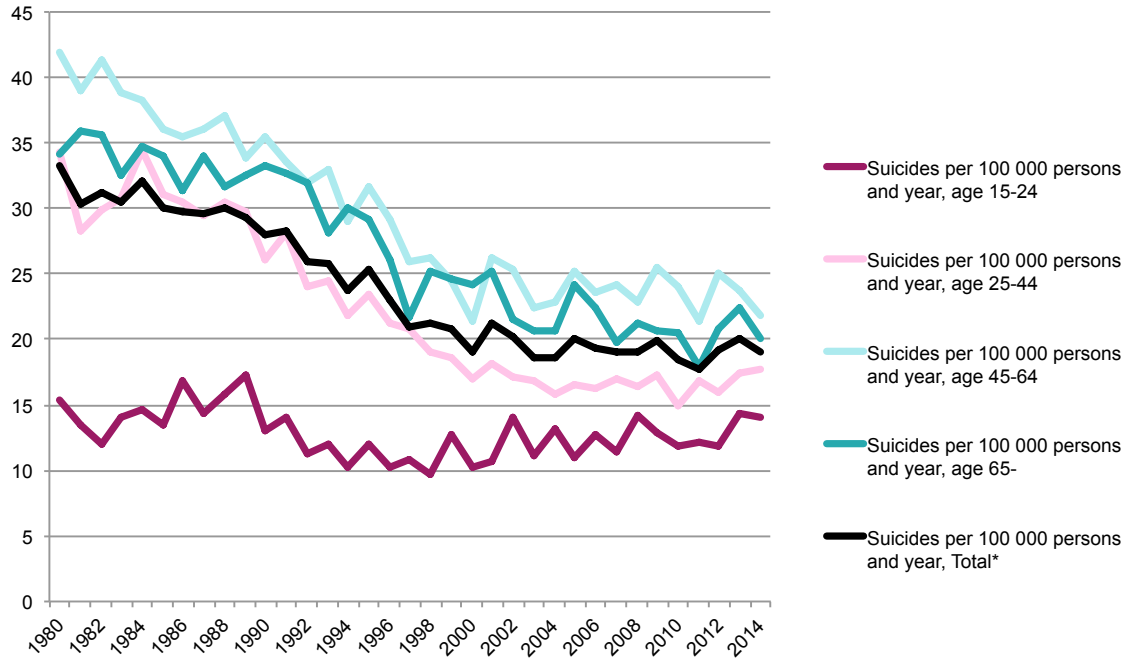
1.3.1 In the world

The quality of epidemiological data on suicide varies in different parts of the world. WHO reports that only 60 countries provide good quality registration of suicide data[5]. Suicide rates range from as high as 20 or more per 100 000 in countries like Latvia, South Korea and Russia, to reported rates of only 1 or lower in Egypt, Oman and Kuwait. More men than women commit suicide worldwide. However, China is an exception with slightly higher incidence rates for women. Suicide attempts are generally more common among women. Historic data from the late 19th century and onwards show that suicide rates have declined in several high-income countries[14,15]. Even though there has been an increase in the treatment of suicidal persons over the past decades, incidence rates of suicide attempts seem to have remained largely unchanged globally[16].

1.3.2 In Sweden

Suicide rates have declined in Sweden from 1980 in all age groups over 25 years but the rates have stagnated in the last decade (Figure 1.1). The reason for the observed decrease of suicides is unclear. A common theory is that the development of better and more accessible treatment for depression has lowered the suicide rates[17-19]. Studies have shown that education of general practitioners in how to treat depression can reduce suicide rates[20,21]. However, restricted to merely naturalistic studies it is impossible to determine which parts of the treatment that have causal relationship with the reduction of suicides.

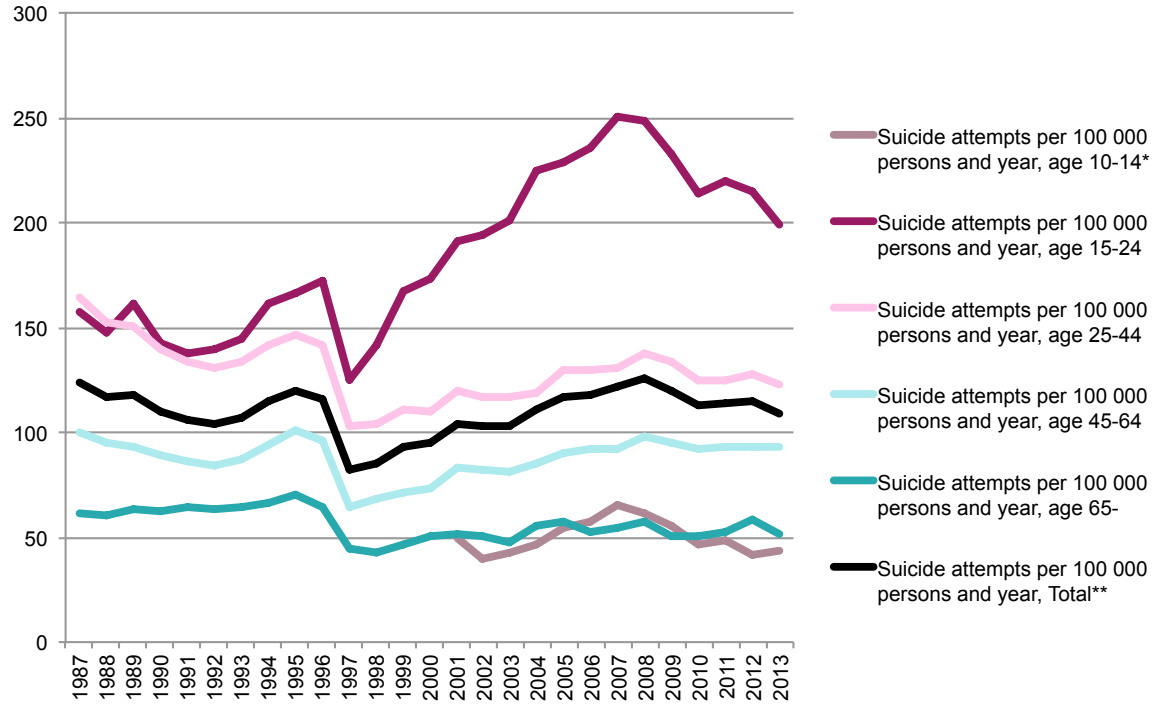
Figure 1.1. Suicides in Sweden per 100 000 persons by age group and year 1980-2014, all certain and uncertain suicides are included, data taken from the National Board of Health and Welfare



** Total include all suicides among 15-year-olds and older. Suicide before the age of 15 is rare and the inclusion of that age group in the Total would make it misleading as a reference point.*

The rate of suicide attempts resulting in hospitalisation in Sweden has been steady for all age groups, except for the age group 15-24, since the late 1990s (Figure 1.2). The rise of attempts in this young group was due especially to an unexplained rise in poisonings[22]. A corresponding rise in suicides in this age group was however not seen, and the trend has declined since 2007. The steep fall of attempts in 1997 was perhaps due to changes in routines surrounding the registration of attempts following a shift from the ICD-9 codes to the ICD-10.

Figure 1.2. Suicide attempts registered in inpatient care in Sweden per 100 000 persons by age group and year 1987-2013, data taken from the National Board of Health and Welfare



** Data only available from 2001 to 2013.*
*** Total equals the mean for the age group 15 years and older.*

1.4 RISK FACTORS FOR SUICIDAL BEHAVIOUR

Several risk factors for suicidal behaviour have been identified. A risk factor is a marker known to be associated with an increased risk. Proven causal relationships are not necessary between the risk factor and the outcome. For instance, the strongest risk factor for suicide is a previous suicide attempt. It is theoretically possible that an attempt in itself contributes to the causal pathway of completed suicide, but another plausible explanation could, in many cases be that both the nonfatal attempt and the completed suicide are caused by common factors.

Risk factors for suicidal behaviour can be divided in distal and proximal[23]. Distal risk factors reflect constitutional traits and include genetic vulnerability, personality, effects of early traumatic events and neurodevelopmental and neurobiological disturbances. Distal risk factors are sometimes called static risk factors since they cannot be changed or treated. Proximal risk factors are factors reflecting a current state and are at least to some extent still

possible to influence, such as psychiatric and somatic disorders, on-going psychosocial or financial problems, and the availability of means to act on a suicidal impulse. Proximal risk factors are also called dynamic risk factors.

1.4.1 Distal risk factors for suicide

1.4.1.1 Heredity

There is plenty of evidence from epidemiological studies that suicidal behaviour run in families, independent from the heredity of psychiatric disorders[24-26]. The rate of suicide has been shown to be twice as high in families of suicide victims as in compared families[27]. The familial effect comes from both genetic dispositions and shared environmental factors[28,29]. Some genes related to the serotonergic system in the brain have been associated with violent suicidal behaviour[24,30], but the findings are inconsistent between studies[31]. The predominant theory is that there are two separate dispositions associated with suicidal behaviour that can be transferred from parent to child; the disposition for depression and the disposition for the trait impulsive aggression[32,33]. These dispositions can be transferred both genetically and through shared environment.

1.4.1.2 Perinatal circumstances

Restricted foetal growth and young maternal age (teenage motherhood) have been linked to elevated risk of suicidal behaviour later in life[34].

1.4.1.3 Country of birth

Suicide rates differ between countries, and when people migrate from their country of birth the risk of suicide tends to follow them on a population level[35,36]. Some studies show that the suicide rates often increases after migration[36].

1.4.1.4 Early traumatic events

Early traumatic life event is a known risk factor for later suicide[23], and exposure to violence in childhood is associated with later suicidal behaviour[37]. Also, bullying victimisation increases the risk for suicidal behaviour as an adult, even after adjustment for psychiatric comorbidity[38,39].

1.4.1.5 Personality

All defined personality disorders in the DSM-system are associated with elevated risk of suicidal behaviour[23,40,41]. Lifetime incidence of suicide in borderline personality disorder is somewhere between 5-10% and 70% attempt suicide at some point[42-44]. Young men with antisocial personality disorder have a nine times higher risk of suicide than other young men. Narcissistic personality disorder has also been connected with increasing numbers of suicide attempts among suicide attempters[45]. Borderline and antisocial personalities share measurable traits such as impulsivity aggression and emotional dysregulation, which are associated with suicidal behaviour[46]. Borderline personality disorder is also strongly associated with NSSI.

Personality is defined as traits that are stable across time, making personality disorder a static risk factor by definition. However, several forms of psychotherapies have shown good results in modifying self-destructive behaviour in borderline[47,48], contradicting this preconception.

1.4.1.6 Sexual orientation

Reviews have shown that suicidal behaviour is more prevalent in lesbian, gay, bisexual and transgender populations[49,50]. This is probably due to effects of the alienation and discrimination that these minority groups still experience in many societies.

1.4.1.7 Religious beliefs

Religion seems to have a protective effect against suicide in both western and eastern countries, especially among people 45 years and older, and in societies with religious homogeneity[51].

1.4.1.8 Neurobiological disturbances

There are several findings of biological markers associated with suicidal behaviour. Already in the 1970s Åsberg and co-workers found that low level of 5-HIAA in the cerebrospinal fluid was associated with violent suicide attempts[52,53]. Since then, the serotonin system has been further investigated, but the true nature of the association has yet to be mapped out[26]. Furthermore, associations between suicidal behaviour and changes in the HPA-axis[54], oxytocin-levels[55] and the immune system[56] have also been reported. A recurrent difficulty within the research field is how to determine whether a found neurobiological disturbance is a trait or a state. The fact that some medical treatments seem to be associated with reduction of suicide risk implies that theoretically, some neurobiological disturbances could be considered as proximal risk factors, rather than distal.

1.4.2 Proximal risk factors for suicide

1.4.2.1 Psychiatric disorders

Many psychiatric disorders are associated with increased risk of suicidal behaviour[57]. Psychological autopsy studies have shown that at least 90% of all suicide victims suffered from at least one psychiatric disorder at the time of death, the most common disorder being depression, present in 50-80% of the cases[58-60]. To suffer from an anxiety, mood, impulse-control or substance use disorder is predictive of suicide attempts[61].

Depression is the psychiatric disorder that is most strongly associated with the risk of suicide. Earlier studies of long-term risk of suicide in depressed patients who had been treated in psychiatric inpatient care noted that almost 15% later committed suicide[62]. In more recent studies of patients with depression receiving outpatient care, the figure is lower; approximately 2%[63]. The prevalence of major depression during one year in adults aged 18 or older in a large national survey made in the US in 2013, was 6.3%[64] and WHO states that depression is the leading cause of disability for both men and women world-wide. Highest

prevalence of depression among suicide victims is seen in women and the elderly[58,59]. An even larger proportion of suicides are associated with at least some depressive symptoms even if another primary disorder also exists. The association between bipolar depression and bipolar disorder in general will be further discussed in relation to study I in this thesis.

Schizophrenia is a psychotic disorder characterised by disturbed perception of reality. The lifetime risk of suicide in schizophrenia is currently estimated to 5% in a large review[65]. Risk factors for suicide in schizophrenia are similar to those in the general population[66]. Comorbidity with depression is one of the major risk factors for individuals with schizophrenia[67]. The only consistent protective factor for suicide in schizophrenia is adherence to effective treatment[65].

Anxiety disorders and the role they play in the development of suicidal behaviour have previously been overlooked. However, Sareen and co-workers found in 2005 that anxiety disorders are independent risk factors for suicide attempts[68]. When anxiety disorders coexist with mood disorders the risk is elevated further.

Anorexia nervosa is an often chronic and disabling eating disorder with one of the highest premature death rates of all psychiatric disorders[69]. Standardised mortality ratios (SMR) above 50 for suicide in anorexia nervosa have been reported in several studies[70], even though a lower SMR (13.6) has been reported in a Swedish register-based study[71]. Comorbidity with mood and anxiety disorders contributes to the high mortality rates.

Substance use disorders include both abuse and dependency diagnoses for alcohol and all other addictive substances. To suffer from a substance use disorder is a risk factor for suicidal behaviour when compared with risk in the general population[72-74]. Especially alcohol and opioid dependency have been linked with elevated suicide rates[74,75]. In the Lundby Study, a longitudinal study of a general population cohort in southern Sweden, 10.5% of the participants with diagnosed alcohol use disorder had committed suicide after a follow-up period of 50 years[76]. Alcoholism and other substance use disorders are common together with other psychiatric disorders. A recent population study from Denmark showed no further increase of risk for suicide in schizophrenia, bipolar disorder and depression when substance use disorder coexisted[77]. However, all-cause mortality was significantly elevated.

1.4.2.2 History of suicide attempt

The strongest known risk factor for suicide is a previous suicide attempt[23,40,41,78]. The risk is highest soon after the attempt but continues to be significantly elevated even decades later[79]. Approximately half of all people who die by suicide have made at least one previous attempt[80,81]. Among the young, the proportion is even larger[60]. In the year prior to their death from suicide, 15-20% of all who committed suicide visited a hospital in connection with a suicide attempt in a large study based in the UK[82]. In a register-based Swedish study of more than 20 000 suicides, 23% of men and 31% of women had been admitted to psychiatric inpatient care within a year of the suicide[83].

In connection with a nonfatal suicide attempt, the presence of a diagnosed psychiatric disorder increases the risk substantially for completion in the future[79,84].

1.4.2.3 Psychiatric hospitalisation

There is an increased risk for suicide associated with psychiatric inpatient care, both during and shortly after discharge[85,86]. The elevation of risk has not been shown to be connected with the hospitalisation per se, and could probably be attributed to factors leading to hospitalisation, such as onset or exacerbation of psychiatric disorders and suicide attempts[87].

1.4.2.4 Somatic disorders

Many somatic disorders, such as cancer, coronary heart disease and stroke are associated with elevated risk of suicide. However, clinical depression is a very common confounder, both partly caused by the somatic disorder, and causally linked to suicide[88].

1.4.2.5 Economic crisis

The French sociologist Émile Durkheim was the first to point at a link between changes in the economy in a society and the rates of suicide[89]. An association has also been confirmed in recent research[90,91]. Elevated suicide rates among young people with low level of education have been found during economic crises[92], but the nature of the relationship between economy and suicidal behaviour remains largely unknown. The economic crisis in Greece during the 2000s, is associated with an increase of the suicide rates in the country[93]. Some evidence indicates that the austerity-related actions causes the elevation of the suicide rate[94].

1.4.2.6 Adverse psychosocial events

Social problems on a personal level, such as divorce, loss of job and other adverse life events can elevate the risk of suicidal behaviour in a short-term perspective[80,95]. These psychosocial risk factors are associated with psychiatric risk factors but are also independent risk factors. The causal direction is sometimes bidirectional. For instance, dramatic life events, such as imprisonment or hospitalisation can trigger other adverse psychosocial events to happen.

1.4.2.7 Availability of means to commit suicide

Evidence shows that the availability of different means to commit suicide affects suicide rates. When the amount of carbon monoxide in domestic gas was reduced in England and Wales in the 1960s, a decline of suicides was observed[96]. When the access to pesticides was limited in parts of rural China, where suicide by ingestion of pesticides account for as much as 60% of all suicides, a decrease in suicide rates was observed[97].

1.4.3 Risk factors exclusive for suicide attempts

The most frequently reported differences in risk factors between suicide and suicide attempts concerns age and sex. Being young and female is linked with a proportionately higher risk of suicide attempts even though the risk for completed suicide is not[23]. In many studies, several

more risk factors for suicide attempt are identified than for suicide since it is a much more common outcome and hence easier to study with sufficient statistical power. With the examples of age and sex in mind, it is important to be cautious with translating findings about risk factors for suicide attempts into risk factors for suicide.

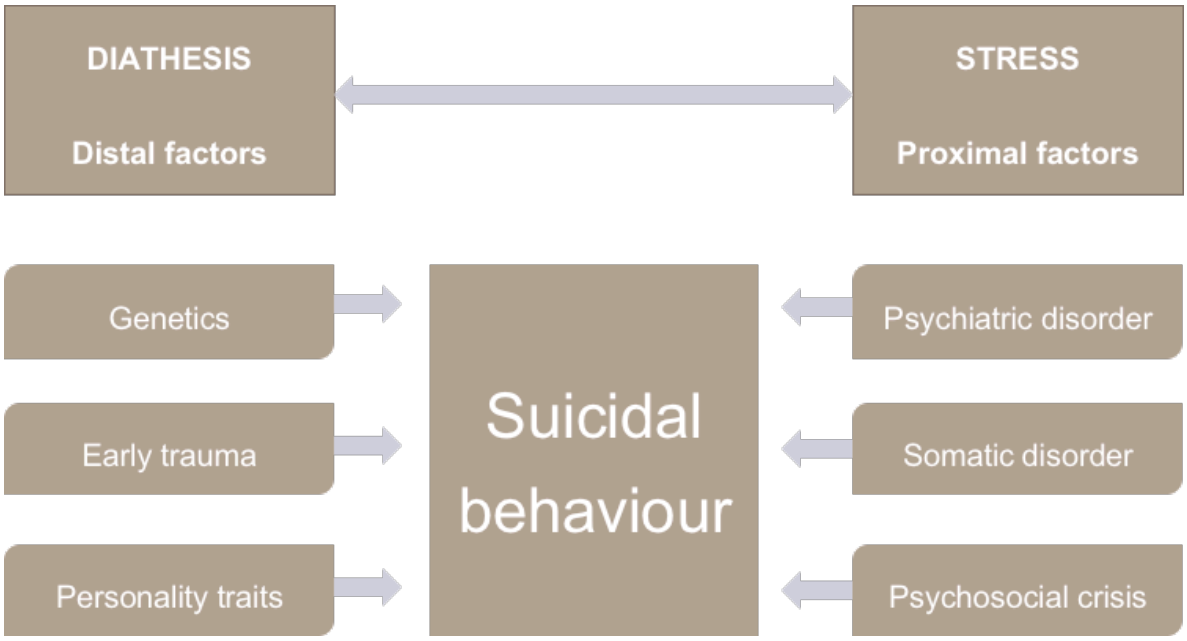
1.5 MODELS FOR UNDERSTANDING SUICIDAL BEHAVIOUR

Several models with the aim to conceptualise the origin of suicidal behaviour have been proposed. Some of the most influential will be described.

1.5.1 A stress-diathesis model of suicidal behaviour

A clinical stress-diathesis model suggested by John Mann proposes a way to understand the complexity of the causes of suicidal behaviour[98]. The model displays suicidal behaviour as an end-result of the balance between pre-dispositional vulnerability and current stress from life experiences. The model is theoretical and implies that any person can engage in suicidal behaviour in particularly stressful situations. This is theoretically possible but empirically not at all established. The benefit of the model is the pedagogical way of displaying how distal and proximal factors need to interact to cause suicidal behaviour.

Figure 1.3. The stress-diathesis model for suicidal behaviour by Mann, 2003 (modified)



Other versions of stress-diathesis models have been proposed. The model by Williams and Pollock emphasises on cognitive aspects, and Jollant and co-workers have proposed a neurobiological model[99].

1.5.2 Maris' general model of risk factors and protective factors

Maris has developed a general model of suicidal behaviours[41]. In this model, predisposing factors, risk factors, protective factors and trigger factors are distinguished from each other and divided into four domains; psychiatry, biology, psychology and sociology. One merit of Maris' system is that it clearly shows the different possible targets for prevention, labelled as primary, secondary and tertiary prevention. Many of the factors in the model interact with each other. Importantly, the model implies that optimised suicide prevention must be a cross-disciplinary endeavour.

Figure 1.4. Maris' general model of suicidal behaviours (modified)

	PRIMARY PREVENTION	SECONDARY PREVENTION		TERTIARY PREVENTION
	Predisposing factors	**Predictor/ Risk factors**	**Protective factors**	**Trigger factors**
Psychiatry/ Diagnosis	History of psychiatric disorder	Diagnosed psychiatric disorder	Effective treatment	Exacerbation of psychiatric disorder Hospitalization Suicide attempt
Biology/ Family history/ Genetics/ Neurochemistry	Age, Sex, Ethnicity Family history of suicide Low 5-HIAA*	Deteriorating physical health	Improved physical health	Acute physical illness Acute pain/nausea
Personality/ Psychology	Adverse childhood experiences	Impulsivity Aggression Suicidal ideation	Hopefulness Cognitive flexibility Coping skills	Hopelessness Notions of death as escape Revenge
Sociology/ Economics/ Culture	Adverse economic or social circumstances	Social, marital or work problems	Social support Marriage Children Religious beliefs	Sudden adverse events Availability of lethal methods Acute stress
	Trait	**State**		**Suicide zone**
Lifespan	**Birth**	**→ Suicidal career**		**Final trigger →Suicide**

** Low levels of 5-HIAA is probably more of a predisposing factor than a trigger factor as Maris suggested in his original model.*

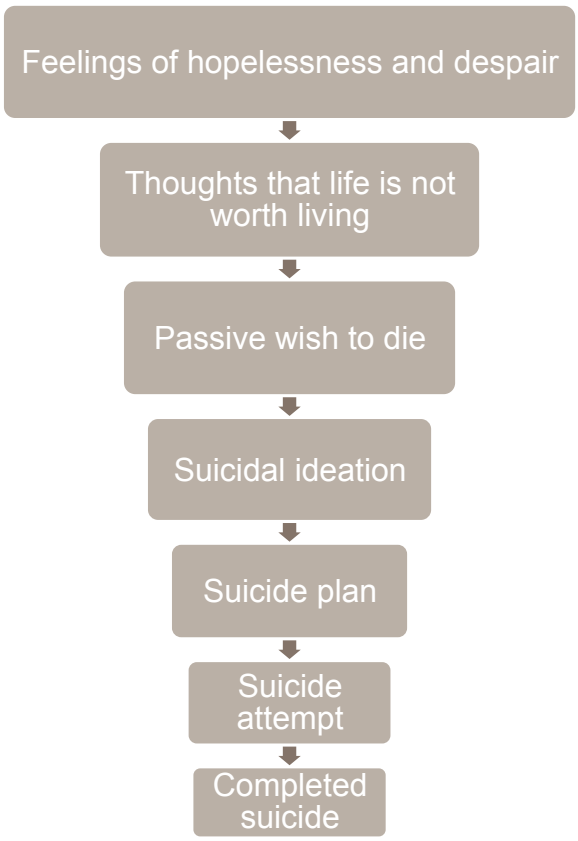
1.5.3 O'Connell's model of the suicidal process

This model was inspired by an earlier model originally constructed by Paykel, who based his model on a study of the prevalence of different forms of suicidal ideation in the general population[100].

O'Connell's model was developed to map the suicidal process in elderly people[101]. There are many similar models with the aim to depict a common pathway from the first thoughts to

final suicide. For instance, a model called “the suicide ladder” by Beskow is often used in Sweden. O’Connell’s model is very similar to Beskow’s but has received more attention internationally. The different stages in the model are not fixed, and the time spent in the different stages can vary from seconds to hours and from days to months, and even years. The model depicts the pathway towards suicide without assumptions of any possible causing factors. When examining a patient, the clinician can use this model to grade how far the suicidal process has evolved. The model can be criticised for over-simplification in proposing a misleading hierarchy between the cognitive and behavioural parts of the process. Instead, these processes could be perceived as parallel, but still interacting, pathways.

Figure 1.5. Model of suicidality by O’Connell et al. 2004



1.5.4 The interpersonal theory of suicide

This theory was developed by Joiner[102] and it hypothesise that the most dangerous form of suicidal behaviour is caused by the simultaneous presence of two interpersonal constructs:

1) the desire to commit suicide, and
2) the capability to engage in suicidal behaviour

The desire for suicide results from two distinct psychological states: thwarted belongingness and perceived burdensomeness, and hopelessness about these states. The capability to engage

in suicidal behaviour emerges, via habituation and opponent processes, in response to repeated exposure to physically painful and/or fear-inducing experiences in life. According to this model, some patients who have an intense desire to commit suicide never will because of lacking capability. In a reversed scenario, a person can have the capability but not the desire to commit suicide. Adverse events that induce a desire to die could quickly make this person very suicidal. According to this model, exposure to violence and nonfatal suicide attempts can be seen as experiences that may enhance a person's capacity to engage in suicidal behaviour. Also in line with this model, impulsive and aggressive personality traits could be seen as linked with the capability of committing suicide, and depression is involved in the development of suicidal desire.

1.6 SUICIDE PREVENTION STRATEGIES

The 19th century German pathologist Rudolf Virchow's famous statement that politics is nothing but medicine at a larger scale is applicable to the field of suicide prevention. To be able to effectively address the problem with suicide, not only psychiatric health care practices needs to be involved.

Suicide prevention includes a broad array of interventions aimed at lowering suicide rates. National strategies exist in 28 countries[5]. The strategies typically include a range of measures such as identification of people at risk, restriction of means, guidelines for media, reduction of stigma and rising of public awareness, as well as education for health care professionals, social workers and police. They usually also include crisis intervention strategies with guidelines for what to do if a suicide occurs.

In 2015 the Public Health Agency ("Folkhälsomyndigheten") was assigned by the Swedish government to coordinate all work in the field of suicide prevention at the national level. The main purpose is to develop and strengthen knowledge management in all instances working with suicide prevention.

Prevention efforts at the community level are called primary prevention and aim to prevent initial development of suicidal behaviour. It can consist of, for instance, efforts to strengthen protective factors to increase resiliency towards suicidal behaviour. Secondary and tertiary prevention aims at lowering risk by interventions on the individual level. Secondary suicide prevention consists of direct interventions towards people at risk to prevent development of suicidal behaviour. This can be done by, for example, effective treatment of a suicidal patient. Tertiary suicide prevention consists of efforts to reduce the risk of suicide among people who have already started to engage in suicidal behaviour.

The work included in this thesis aims to contribute to suicide prevention by addressing questions about how to better identify people at highest risk. The suicide risk assessment is central to this process.

1.6.1 Suicide risk assessment

To make suicide risk assessments is one of the most important and difficult tasks in psychiatric practices. The resulting evaluation heavily influences the decision making process of a clinician. In common practice, the clinical assessment procedure consists of gathering relevant information based on knowledge about risk factors for suicide, and an overall evaluation of the patient's condition. Many researchers have reached the conclusion that it is not possible to predict suicide with a sufficient amount of certainty[103-105], and a recently published report in Sweden states that no reliable assessment tools are available[106]. However, one problem with scientific evaluations of suicide risk assessments is that for ethical reasons, they are always made in naturalistic clinical settings, where a patient's report of serious suicidal ideation and behaviour will cause a response from the health care provider aiming at preventing suicide. In other words, being identified as a high-risk patient normally activates preventive efforts that may lower the risk. Hence, even though it is true that prediction of suicide is difficult on a general population level, it must not lead to a resigned attitude towards individual risk assessments made in everyday clinical work.

Many tools and scales have been developed to facilitate or structure the suicide risk assessment process. All scales are based on assumptions about which factors that are of most relevance. Some scales have been tested as prediction tools. When evaluating a scale's predictive properties it is important to identify:

1) what outcome it claims to predict (completed or attempted suicide?)
2) what time-frame it uses (short or long-term prediction?)
3) for whom it applies (general public screening, psychiatric patients or suicide attempters?)

The predictive properties are best described by measures of sensitivity and specificity. The sensitivity of a predictive test is the probability that the test correctly identifies those with the outcome. The specificity of a test is the probability that the test correctly identifies those without the outcome. These measures together with a known prevalence of the outcome are sufficient to evaluate the predictive value of a scale.

1.6.1.1 Scale of Suicide Ideation (SSI)

The Scale for Suicide Ideation was developed by Aaron T Beck and co-workers in 1979 to quantify the intensity of suicidal ideation. It consists of 21 questions, and has a maximum score of 38. Psychiatric outpatients who scored 16 or above at their worst time point had an odds ratio of 13.8 to commit suicide within a mean follow-up period of 4 years[107].

1.6.1.2 Suicide Intent Scale (SIS)

SIS is developed for use after a suicide attempt and focuses on aspects indicating high level of intention to die from the attempt. It comprises 15 questions with a maximum score of 30. A Swedish follow-up study from 2012 found a positive predictive value of 16.7% for predicting suicide within up to 9 years after the attempt[108].

1.6.1.3 Suicide Assessment Scale (SUAS)

SUAS was developed by Stanley and co-workers to capture observed and reported symptomatology considered to be related to suicidal behaviour. It was constructed to be sensitive to changes over time. It consists of 20 questions with five answering levels from 0 to 4. Maximum score is 80 points. In one study of suicide attempters, having a score of ≥39 generated a positive predictive value of 19.4% for suicide[109]. In another study using the cut-off ≥30, a sensitivity of 79% and a specificity of 68% were reported for predicting a new suicide attempt[110].

1.6.1.4 SAD PERSONS Scale

SAD PERSONS Scale is an inventory of ten yes/no-questions related to risk for suicidal behaviour. The name is an abbreviation of the first letter of every question: Sex (male?), Age (high?), Depression, Previous attempt, Excess alcohol or substance use, Rational thinking loss, Social support lacking, Organised suicide plan, No spouse, Sickness. Maximum score is ten. In one study[111] using the cut-off ≥7, a deliberate self-harm event was predicted within six months with a specificity of 96.8%. The problem was that the sensitivity was no more than 6.6%. Another study by Bolton and co-workers came to a similar conclusion[112]. The scale misses an overwhelming majority of all whom self-harm, making it unsatisfactory as a tool for prediction in a clinical setting.

1.6.1.5 Columbia Suicide Severity Rating Scale (C-SSRS)

Posner and co-workers at Columbia University, NYC, have developed a scale that has quickly become the gold standard for screening of suicidal ideation and behaviour in the US. It is now required in clinical trials according to the FDA. The scale consists of two parts: the first rates the severity and intensity of suicidal ideation and the second part classifies suicidal behaviour. The scale provides definitions of different suicidal behaviours, separating actual suicide attempts from non-suicidal self-injury, interrupted suicide attempts, aborted suicide attempts, and preparatory suicidal behaviour.

The predictive properties of the scale have not been fully investigated. However, in the first study published using the C-SSRS, the participants with the two highest levels of ideation severity (with suicide intent or with suicide intent and a plan) at baseline had higher odds for attempting suicide during the follow-up[113]. This finding led to the recommendation that all patients screened with C-SSRS who reach that level of severity should be referred to a psychiatric unit for evaluation. One later study based on C-SSRS also found that severity of suicidal ideation increased risk for suicide attempts independently, even when adjusted for age, sex, socioeconomic status, lifetime NSSI and suicide attempts[114]. An electronic version of the scale has also been validated[115] and a larger study using this version has replicated the strong association between that same degree of suicidal ideation and a risk of suicidal behaviour within a mean follow-up period of 64 days[116].

The C-SSRS is not a summative scale, hence no overall threshold scores can be distinguished. Yet, the scale's distinctions of suicidal ideation and behaviour can be useful in research combining information from the scale with other clinically relevant factors. The outcome of future research will decide the fate of C-SSRS.

1.7 HIGH-RISK POPULATIONS FOR SUICIDE

Based on our knowledge of prominent risk factors for suicide, some high-risk populations are clinically possible to identify. However, the vast majority of people within any of these high-risk groups will not commit suicide or engage at all in suicidal behaviour. There is also a possibility that risk factors have different importance within different high-risk groups. We need to learn more about differentiating risk within high-risk groups, which is the purpose of the studies in this thesis. I will introduce the high-risk groups with descriptions of patients I have met in my clinical work. Details in the stories have been changed to protect the patients from identification.

1.7.1 Bipolar patients

Miguel - a bipolar patient who committed suicide

I met Miguel when I was working as a physician in a psychiatric ward in Stockholm. He was born in Portugal and had moved to Sweden after meeting his wife 10 years earlier. They had two children, 3 and 9 years old. His wife brought him to the hospital because he had become depressed, lying in bed, not being able to work. The reason why they came in that particular day was that the wife had found Miguel in the garage trying to tie a knot with a rope. When asking why, he gave an answer that wasn't convincing, his wife became scared and after some persuasion he voluntarily followed her to the hospital. On the ward, Miguel was almost mute and seemed severely depressed. At first, no previous history of depression was known, and he continued to deny that he had ever had suicidal intentions. Due to the depth of his depression, ECT was considered. However, blood tests revealed an autoimmune thyroiditis. Endocrinologists were consulted and he received treatment. The symptoms of depression did not respond to this treatment and antidepressants were also introduced. After talking with Miguel's parents in Portugal over the phone, the clinical picture became more complicated. They could describe that Miguel had had at least three depressions in his early life, and that he had tried to commit suicide by hanging at least once, more than 15 years ago. They also told us that he had been in hospital once because of a manic state. When talking with Miguel about this, he said he never had wanted to mention this to his wife and that he thought that he had got rid of the mental problems by now. Miguel stayed at the ward for three more weeks, and continued to deny all suicidal ideation. He received a mood stabiliser called lamotrigine. The depressive inhibition and his mood slowly improved, and Miguel became more talkative. Contact was established with a psychiatric outpatient clinic specialised in bipolar disorders and Miguel was included in the quality register BipoläR. A month later, it came to my knowledge that Miguel had committed suicide by hanging in the garage one day while his wife and kids were away from home.

What can be learned from Miguel's tragic death? It is extremely important to obtain good information about previous psychiatric episodes and suicidal behaviour in order to be able to make a good risk assessment. In this case, Miguel denying his thoughts of suicide was contradicted by his behaviour and his history, and the risk of suicide was underestimated.

Bipolar affective disorder implies a particular risk for suicidal behaviour[117,118]. Bipolar disorder is an affective disorder characterised by episodes of elevated mood and depressive episodes of varying severity. It is a serious and often disabling disorder associated with reduced life expectancy[119,120]. However, the course of the disorder is unpredictable and the impact on quality of life differs between patients. A review has estimated the risk of suicide in bipolar patients to be more than twenty times higher than in the general population[121]. The risk is even greater among patients who have been admitted to inpatient care due to bipolar disorder[122] and especially high in those admitted after an attempted suicide[79]. A meta-analysis identified that previous suicide attempt and hopelessness were the most important risk factors for suicide in bipolar patients[117]. The main risk factors for nonfatal suicide attempts in bipolar disorder included family history of suicide, early onset of bipolar disorder, extent of depressive episodes, the presence of mixed affective states, rapid cycling, comorbid psychiatric disorders including anxiety, eating and substance use disorders. Bipolar patients who at some point have attempted suicide have an even more increased risk for completed suicide, especially those who use a method other than poisoning[84]. Relational and economic stressors have also been identified as risk factors for suicidal behaviour in bipolar patients[123,124].

Effective treatment for bipolar disorder is nowadays available. The mood stabilising drug lithium has been shown to decrease risk of suicidal behaviour substantially in naturalistic studies[123,125]. There is also evidence that stable access to care in units specialised in bipolar patients is helpful in reducing rates of suicide in this high-risk group[126].

1.7.2 Released prisoners

More than 10 million people are currently held in prison in the world[127]. However, a considerably larger number of released-prisoners are living in society. Since most prison sentences are short, the prevalence of ex-prisoners is several times the total number of prisoners.

Magnus – the difficult transition to a life in freedom

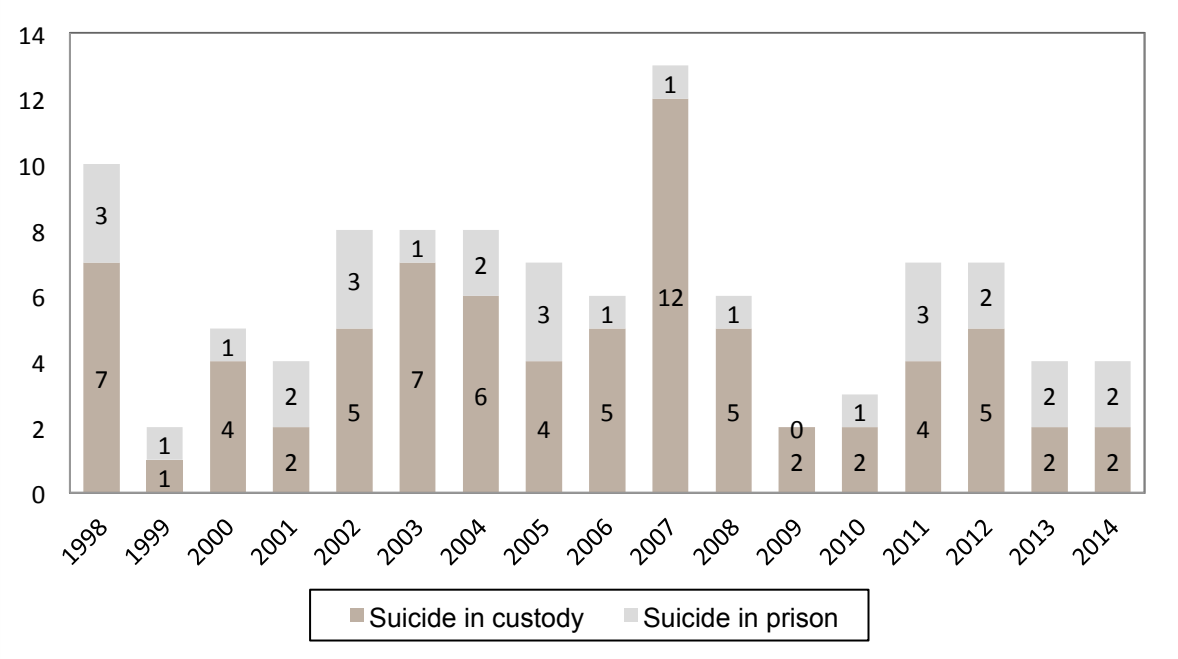
I met Magnus when I was working at the emergency department at Södersjukhuset in Stockholm one late night in February 2006. He arrived in an ambulance, presenting with pressure over the chest and dyspnoea. He was around fifty years of age, had a large grey beard, plentiful of tattoos all over his body, large biceps and a few extra pounds around his belly. He seemed very scared. There were no signs of pathology on the ECG, and nothing abnormal in his status when I examined him. He reported no previous illnesses and no on-going medication. After a short interview, I understood that he had experienced a panic attack. After reassuring information he calmed down and I asked him if there was any event or circumstances that may have triggered this reaction. He then told me that he had been released from prison one week earlier, after being imprisoned for over ten years. "For murder", he added shamefaced. The first week in freedom for over a decade had been difficult. Before going to prison he abused both alcohol and amphetamine regularly, but he had managed to quit and was determined not to fall back in his old habits. He now stayed at a friend's house, but he had developed insomnia and felt a rising hopelessness. Asking about suicidal thoughts he told me that he had

considered it many times over the years but never acted on it. When the current panic attack started he had got a sudden impulse to jump from a window to end his life but his friend obstructed him and called for an ambulance instead. From a medical point of view, Magnus was free to go but given his fragile situation and lack of health care contacts, I persuaded him to accept being referred to a psychiatric clinic to stay overnight. I do not know what happened to Magnus after that night, but his case illustrates how difficult the adjustment to life outside prison can be.

There are 48 correctional facilities for sentenced adult prisoners (≥18 years) in Sweden and more than 10 000 persons (7% women) started serving their prison sentences each year during 2005–2009[128]. These prison sentences constituted 22% of all convictions during this years, while other forms of penalties such as fines, different forms of probation, and conditional sentences predominated[129]. The prison population rate in Sweden is 67 per 100 000 of the national population[127]. This is similar to other Scandinavian countries, but lower than both the world average (144) and that in Australia (130), Netherlands (82), England and Wales (148), and the US (716) where previous studies of suicides in released prisoners have been conducted[130-133].

In Sweden, the number of suicides occurring in custody, among detainees awaiting trial, is high compared with suicide rates among sentenced prisoners[134]. However, the suicide rates among sentenced prisoners have been on an equal level to the general population, indicating that the prison time after sentence is less of a risk period in the life of criminal individuals in Sweden. However, little is known about the risk of suicide after release from prison.

Figure 1.6. All suicides in custody and prison in Sweden 1998–2014



A systematic review[135] of suicide after release from prison found that all existing studies reported elevated standardised mortality ratios[130-132]. Studies from Australia and the US have demonstrated particularly high suicide rates during the first weeks after release, suggesting that this is a high-risk period[133,136]. Hence, suicide in recently released prisoners has been labelled a high-risk population and has become a part of national suicide prevention strategies in a few western countries.

1.7.3 Suicide attempters

One of the most common reasons for visiting a psychiatric emergency department is a suicide attempt. The strong association between suicidal behaviour and psychiatric symptomatology motivate an instant psychiatric evaluation.

Maria – a violent suicide attempter

Maria arrived at the psychiatric emergency room at St. Göran's hospital in the company of two policemen, who had found her standing outside the handrail on a bridge in central Stockholm. She had resisted violently against coming with them, screaming that she wanted to be left so that she could jump to kill herself. When the police had left, she calmed down and was willing to talk with me. She was 20 years old and had no previous psychiatric contacts. That night she had been out drinking with some friends, and on her way home she had been overwhelmed by feelings of hopelessness, suddenly feeling an urge to die. She told me that this wasn't the first time she had felt like this, but she had never made a suicide attempt before. She showed me scars on her arms that she had inflicted to herself just a few days earlier "to relieve anxiety". Further in the interview she told me that she recently had broken up with a man who had beaten her repeatedly "just as my dad used to do". Maria was offered to stay overnight and she accepted. A few days later I read in her medical records that she had made a violent suicide attempt on the ward by cutting herself with a hairpin.

The case of Maria exemplifies how interpersonal violence and different acts of deliberate self-harm can seem to be intertwined.

Suicide attempt is the strongest known risk factor for later suicide[23,79]. Approximately half of all people who die by suicide have made at least one earlier attempt[80,81]. In the year before their death from suicide, 15-20% visited a hospital in connection with a suicide attempt in a large study from the UK[82]. In a register-based Swedish study of more than 20 000 suicides, 23% of men and 31% of women had been admitted to psychiatric inpatient care within a year of the suicide[83]. Mortality after previous suicide attempts is high in general, not only from suicide. In a study from Norway, with a very long follow-up period after self-poisonings, 37.5% of all participants died within 20 years, 7% by suicide[137]. The risk of death from all causes was significantly elevated.

There are circumstances associated with suicide attempts that may indicate an even higher risk for future completion. Suicide attempters with bipolar disorder or psychotic disorder have a more pronounced elevation of risk, as do attempters who use violent methods such as hanging or use of firearms[84]. Violent suicide methods are also associated with higher levels of

lifetime aggression[138]. Mutual causal pathways to aggressive and suicidal behaviour have been suggested to involve personality traits, such as impulsivity and aggression[46]. These traits are in turn related with occurrence of interpersonal violence, both as a victim and as a perpetrator. Hence, it is theoretically plausible that experiences of interpersonal violence may serve as a marker for a co-occurring tendency for suicidal behaviour. Some evidence point in this direction[139,140] but more clinical research is needed to illuminate the nature of the association.

Suicide attempters clearly constitute a high-risk group for repeated suicidal behaviour. To make prevention (i.e. efforts to prevent escalating suicidal behaviour) more effective, we need to improve risk assessment of this group.

2 AIMS

The overall aim of the thesis has been to identify risk factors for suicidal behaviour within three different high-risk populations for suicide. The intention is to enhance suicide prevention efforts by increasing knowledge in the field of suicide risk assessments.

The specific aims for the included studies were:

Study I – To investigate risk factors for suicide attempts among bipolar patients. Our hypotheses were that recent affective episodes, recent psychiatric inpatient care, early onset of psychiatric problems, family history of affective disorder, comorbidity, complicating social factors, and violent behaviour predict suicidal behaviour in bipolar patients, and also that risks of attempted suicide differ between subtypes of bipolar disorder.

Study II – To investigate risk factors for suicide among released prisoners. Our hypotheses were that in released prisoners 1) the first 28 days after release imply the highest risk for suicide, 2) previous suicide attempt, psychiatric disorder and violent crime is linked to suicide and 3) there is a difference in risk factors for suicide compared with general population controls.

Study III – To investigate the ability of the KIVS to predict repeated suicidal behaviour within six months. Our hypothesis was that information about interpersonal violence collected using the KIVS could predict repeated suicidal behaviour within six months after a suicide attempt.

3 METHODS

In the three papers included in this thesis we have studied risk factors for suicidal behaviour in three different high-risk populations for suicide. The study populations are defined in different ways. In study I it is defined through a common diagnosis, in this case bipolar disorder, and by the patient's inclusion in the quality register BipoläR. The population of released prisoners in study II is ultimately defined by decisions from the judicial apparatus, and by the appearances in the Crime Register. In study III, having engaged in certain behaviour, in this case a nonfatal suicide attempt, and subsequently visiting one of three included emergency departments, defined the population.

Table 3.1. Descriptions of the three high-risk populations included in this thesis.

	Study I	Study II	Study III
Participants	Bipolar patients	Released prisoners	Suicide attempters
No of participants	6 086	26 985 persons released 38 995 times	355
Potential risk factors studied	Bipolar subtype Suicide attempts Lifetime episodes Recent episodes Inpatient care Early onset Comorbidity Heredity Somatic disorders Social factors Violent behaviour	Suicide attempt Psychiatric morbidity Native-born Any violent crime	Experiences of interpersonal violence as identified with the KIVS
Outcome	Suicide attempts, fatal and nonfatal combined	Completed certain or uncertain suicide	1. Suicide attempts, fatal and nonfatal combined 2. Violent suicide attempts, fatal and nonfatal combined
Outcome source	The national quality register BipoläR	The Cause of Death Register, held by the National Board of Health and Welfare	Medical records
Outcomes corresponding ICD-codes	ICD 10: X60-84	ICD 8-9: E950-9, E980-9; ICD 10: X60-84, Y10-34	ICD 10: X60-84
Follow-up time	Mean total follow-up time was 2.4 years (SD = 1.3)	Median time per release was 451 days	Until death or up to 6 months

All studies are designed as cohort studies. In study II we also used a population control cohort as a complement. By doing so, the design of the study could also be described as a controlled cohort study or even a nested case-control study, where the nest equals all people included in the Total Population Register in Sweden, during the study period. The overall structure of a cohort study may however make the latter denotation misleading.

3.1 STUDY I

3.1.1 Study design and population

Study I is a cohort study using data from the Swedish national quality register BipoläR. This is one of several psychiatric quality assurance registers established in Sweden during the 2000s, and contains data about patients diagnosed with bipolar disorder[141]. All subtypes of bipolar disorder are included in the register and subsequently in our studied cohort. BipoläR contains data from patients who have only been treated in outpatient care as well as those who have at times also required hospital treatment.

Patients who have received a bipolar diagnosis are asked to participate in the BipoläR in connection with visits to their psychiatric outpatient clinic. If they agree, the data is collected by a psychiatrist or other trained staff with access to all clinical data of each patient. After first registration, additional data is collected in annual follow-ups in conjunction with visits to the outpatient clinic.

According to a report from 2013, 50% of all patients with bipolar disorder in Sweden who had received outpatient care for the disorder were included in the register[142]. Of all included patients, 75% had fulfilled at least one yearly follow-up. Since clinicians collect the data with extensive knowledge about the included patients and their disorders, the quality is considered to be high and clinically valid[143].

In study I all patients who were registered in BipoläR between 2004 and 2011, and were followed-up at least once between 2005 and 2012, were included.

3.1.2 Included variables and studied outcome

BipoläR contains variables with data on psychiatric and somatic comorbidity, as well as many other anamnestic details. Table 3.2 shows all explanatory variables included and analysed in this study.

Table 3.2. All potential explanatory variables for suicidal behaviour analysed in study I and how the factors are defined

Explanatory variable	Definition
Previous suicide attempt	Any reported previous suicide attempt in lifetime at inclusion
Bipolar disorder subtype	Type 1 (ICD-10 codes F30.1-30.9, F31.0-31.7) Type 2 (F31.8) Not otherwise specified (F31.9) Schizoaffective disorder of bipolar type (F25.0)
Affective episodes during the year before inclusion	Includes any affective episode (depressive, hypomanic, manic or mixed)
Four or more specified lifetime affective episodes	Depressive, hypomanic, manic or mixed episodes
Family history of affective disorder	Bipolar disorder, unipolar disorder or dysthymia in first-degree relatives
Psychiatric inpatient care during the year before inclusion	Inpatient care under any diagnosis
Early onset of psychiatric problems	Any psychiatric disorder before 18 years of age
Psychiatric comorbidity	Substance use disorder (ICD-10 codes F10-19; F55) Non-organic psychoses (F20-29 except F25.0; F53.1) Anxiety disorders (F40-48; F62) Eating disorders (F50) Personality disorders (F60-F61; F68.8)
Complicating somatic disorder	Any complicating somatic disorder
Complicating social factors	Family-, work, or economy-related problems
Violent behaviour	Violent behaviour directed towards other people

The outcome variable in this study is suicidal behaviour during follow-up, as registered in the BipoläR. During the follow-up, patients were asked if they had made one or more nonfatal suicide attempts during the year since last report. Also attempts already known to the clinician but not mentioned by the patients, and all suicides, were reported to the register. Hence, the outcome is defined as one or more fatal or nonfatal suicide attempts during the year before each annual follow-up date. The definition of attempted suicide in the BipoläR is corresponding to the ICD-10 category intentional self-harm (X60-84).

3.1.3 Statistical analyses

The explanatory variables presented in Table 3.2 were all analysed as dichotomous variables with chi^2-test and Fisher's exact test. The variables that predicted an attempt were included in the next step, a multiple logistic regression model. The model was adjusted for age, a potential confounder. Odds ratios were calculated with 95% confidence intervals. One

additional multiple logistic regression model was used to study subcategories of possibly complicating social factors. This model included factors related to primary group, school, work, social environment, housing, economy, healthcare and criminal behaviour. Previous suicide attempt was only used as an explanatory variable and not as a covariate to be adjusted for, since it may be on the causal pathway from the other studied risk factors.

The results in study I were all stratified by sex, except when sex was used as an explanatory variable. Due to differences in early versions of the register, data for some of the used variables were only available for subsets of the cohort. The statistical software SPSS version 22 was used for all statistical analyses.

3.2 STUDY II

3.2.1 Study design and population

Study II is a cohort study following all released prisoners in Sweden between January 1, 2005 and December 31, 2009. To avoid inclusion of legally innocent people, we did not include those released from custody without a prison sentence. All members of the cohort were followed from release until suicide or other cause of death, emigration, new incarceration or December 31, 2009. With our design, we focused on the time in freedom after release, making participants disappear from the cohort if they were incarcerated again, and allowing them to reappear again in the cohort, if they were released again within the study period. To be able to calculate incidence rate ratios, we used ten general population controls per released prisoner, matched on sex and age. The controls could not have been convicted to prison by the date of the corresponding cohort member's release. If a member of the control group was convicted to a prison sentence during the study period, that person ceased to contribute to time under risk in the control group. If that same individual was released within the study period, he or she reappeared as a member of the studied cohort instead.

3.2.2 Sources of data and included variables

Sweden and other Scandinavian countries have a long tradition in maintaining high quality national registers covering the whole population. The unique personal identification numbers given to all citizens play a key role in facilitating population-based health-care research[144-146]. Study II is a study relying completely on data from population registers in Sweden.

Our data was extracted from a large research database called CRIME II constructed at the department of Medical Epidemiology and Biostatistics at Karolinska Institutet. The personal identification numbers were used to link data from different nationwide population registers. The subjects in the research database were de-identified after the linkage so that individual persons were impossible to identify when analysing the data. The registers used in study II are described in Table 3.3.

Table 3.3. Description of Swedish population registers used in study II

Name of register	Held by	Data used in study II
The Prison Register (PR)	The Prison and Probation Services	Dates of incarceration and releases from prison Information about type of crime
The National Crime Register (NCR)	National Council of Crime Prevention	Information about previous prison sentences.
The National Patient Register (NPR)	National Board of Health and Welfare	Psychiatric diagnoses Previous suicide attempts
Total Population Register (TPR)	Statistics Sweden	Information on sex and age of all people in Sweden. Enabling the use of matched controls.
The Cause of Death Register (CDR)	National Board of Health and Welfare	Information about causes of death, including suicide

The inclusion period of the study was limited to five years, since all individuals in the PR are removed five years after their last contact with the Prison and Probation Services.

We defined violent crime in a way previously used in epidemiological research[147]. This includes a broad array of crimes including homicide, assault and robbery, but also threats and violence against an officer, gross violation of a person's integrity, unlawful coercion, unlawful threats, kidnapping, illegal confinement, arson and intimidation. Attempted and aggravated versions of these offences are also included in this definition. Notably, sexual crimes were not included in our definition of violent crime.

The psychiatric variables in the study are based on the NPR including diagnoses from hospitalisations in Sweden since 1973 an onwards, and outpatient, non-GP physician specialist diagnoses since 2001. There can be several diagnoses connected with an episode of hospitalisation or a health care visit in the NPR. There is always one main (primary) diagnosis assigned, and usually a few additional diagnoses. The second assigned diagnosis is called the secondary diagnosis, the third is called the tertiary diagnosis, and so forth. In this study, to be labelled as having suffered from a psychotic or affective disorder, a person needed to have at least one of these diagnoses as a main diagnosis in lifetime. For personality and substance use disorders a secondary diagnosis during lifetime sufficed. The reason for this, is that both personality disorders and substance use disorders most commonly are used as secondary diagnosis, and the prevalence of these conditions would probably have been underestimated in our study otherwise. In the category any psychiatric disorder, at least one main or secondary diagnosis was required.

The explanatory variable previous suicide attempt includes both acts of deliberate self-harm and acts of self-harm with uncertain intent. This is in line with other research using similar register data[148].

Table 3.4. Psychiatric variables analysed in study II and corresponding ICD-codes

Diagnosis	ICD-codes
Psychotic disorder	ICD 8: 295, 297, 298.2-9, 299; ICD 9: 295, 297, 298.2-9; ICD 10: F20-29
Affective disorder	ICD 8: 296.0-3, 296.8-9, 298.0-1, 300.4, 301.1; ICD 9: 296.0-9, 298.0-1, 300.4, 311; ICD 10: F30-33
Personality disorder	ICD 8: 301.1-9; ICD 9: 301.0, 301.2-9; ICD 10: F60-61
Substance use disorder	ICD 8: 291, 303, 304; ICD 9: 291, 292, 303, 304, 305.0-9; ICD 10: F10-19
Any psychiatric disorder incl. substance use disorder	ICD 8: 290-315; ICD 9: 290-319; ICD 10: F00-F99
Any psychiatric disorder excl. substance use disorder	Defined by removing the ICD-codes for Substance use disorder from the definition of Any psychiatric disorder above
Previous suicide attempt	ICD-8-9: E950-9 and E980-9, ICD-10: X60-84 and Y10-34

The studied outcome was completed suicide. To avoid underestimating the rates of suicide, we defined suicide as both certain and uncertain suicides as defined by ICD-codes in CDR, in consistency with other research within the field[149-151].

3.2.3 Statistical analyses

In study II absolute rates of suicide and incidence rate ratios were presented. The prevalence of lifetime psychiatric disorders among the released prisoners were analysed and comparisons with the controls were made using Fisher's exact test. We estimated hazard ratios as a measure of the relative risk for completed suicide with the use of Cox proportional hazards regression modelling. First, we conducted bivariate analyses. The significant non-overlapping predictors from those analyses were then used in a multivariate model. Consistently we used 95% confidence intervals. All analyses were carried out with the use of the statistical software SPSS version 20.

3.3 STUDY III

3.3.1 Study design and population

Study III is part of a multicentre study conducted in Sweden at three psychiatric departments; at St. Göran's Hospital in Stockholm, Sahlgrenska University Hospital in Gothenburg and Umeå University Hospital. Patients presenting to hospital within a week after an act of deliberate self-harm with or without suicide intent were considered for participation. To enable follow-up through medical records, inclusion criteria also included having a Swedish personal identity number, and being a resident of the geographic uptake area of the specific hospital. Patients who were not able to take part in the interview, either due to insufficient language skills or because of acute symptoms interfering with verbal

communication, were not asked to participate in the study. This included persons who were too confused, aggressive, psychotic or demented. Identified patients who met inclusion criteria and no exclusion criteria were asked to participate, and all participants gave written informed consent. Structured interviews were conducted within a week from presenting to the hospital. Specially trained health care professionals conducted all interviews between April 2012 and April 2014. Finally, to avoid mixing suicide attempters with patients committing non-suicidal self-harm, participants who did not have any suicide intent at the index self-harm act were excluded from this study.

3.3.2 Variables and outcome

The interview included a set of background questions and the Karolinska Interpersonal Violence Scale (KIVS). The scale consists of four subscales measuring expressions of violence in childhood (age 6-14 years), expressions of violence as an adult (age 15 years and above), exposure to violence in childhood (age 6-14 years) and exposure to violence as an adult (age 15 years and above). The two subscales capturing interpersonal violence in childhood (age 6-14 years) also include experiences of bullying and bullying victimisation. All subscales are scored from 0-5; 0 corresponding to no experience at all and 5 to experience of severe forms of interpersonal violence. Hence, the maximum total-score on the KIVS is 20. No cut-off score for the full scale has been applied in previous research. To create a clinically useful variable, scores were dichotomised at the median (0-5 vs. 6 and above). The reliability and validity of the KIVS was evaluated buy Jokinen and co-workers in 2010[139].

Studied outcome was a new fatal or nonfatal attempt within six months after index attempt. We used an established definition of suicide attempt, as a potentially self-injurious action for which there is evidence, either explicit or implicit, that the individual intended to kill him or herself. The action may or may not have resulted in injury[11]. In additional analyses we used suicide attempt with a violent method as the outcome, defining violent method as all methods except poisoning; gassing, hanging, drowning, using firearm, cutting, jumping from a height, crashing with a motor vehicle or other specified methods. This distinction between violent and non-violent methods is well established in previous research[52,150,152]. Information about outcome was extracted from the patient's electronic medical records.

3.3.3 Statistical analyses

Logistic regression analysis was used to calculate odds ratios for repeated suicide attempt. The odds ratios represent how risk changes with a one-increment increase on the KIVS total score/subscale. Receiver operating characteristics (ROC) curves were used to further evaluate predictive properties of the subscales and total-score of the KIVS. All statistical analyses were made with the statistical software SPSS Version 22.

4 RESULTS

4.1 STUDY I

4.1.1 Descriptive statistics

The study population consisted of 6 086 bipolar patients. The mean follow-up time was 2.4 years (SD = 1.3). The cohort consisted of 2 408 men and 3 678 women (60.4%). Mean age was 49.3 years (SD = 12.8) for men and 48.3 years (SD =13.0) for women. Thirteen fatal and 338 nonfatal suicide attempts were reported during follow-up. More women than men engaged in suicidal behaviour during follow-up, 6.9% compared with 4.1% of the men ($p<0.001$).

4.1.2 Risk factors for suicidal behaviour in bipolar disorder

Three explanatory variables included in the initial chi^2-tests lacked significant association with the studied outcome: having a schizoaffective disorder of bipolar type, having had 4 or more lifetime manic episodes and having a family history of affective disorder. All other included explanatory variables were associated with the outcome in men or women, or in both sexes. All the significant variables in the initial analysis were included in the multiple regression analysis. The results are presented in table 4.1.

Table 4.1. Explanatory variables in the multiple regression analysis of study I

Explanatory variables	Men	Women
Previous suicide attempt	3.93 (2.48-6.24)	4.24 (3.06-5.88)
Bipolar subtype		
Type 1	Ref	Ref
Type 2	0.96 (0.59-1.55)	1.07 (0.78-1.46)
NOS	1.65 (0.91-3.00)	1.08 (0.71-1.62)
Affective episodes during the year before inclusion	3.63 (1.76-7.51)	2.81 (1.78-4.44)
4 or more lifetime depressive episodes	2.06 (1.08-3.92)	1.93 (1.27-2.94)
4 or more lifetime hypomanic episodes	1.30 (0.80-2.12)	0.91 (0.67-1.24)
4 or more lifetime mixed episodes	1.18 (0.72-1.96)	1.40 (1.02-1.90)
Psychiatric inpatient care during the year before inclusion	3.57 (1.59-8.01)	2.68 (1.60-4.50)
Early onset of psychiatric problems	1.55 (0.88-2.74)	1.50 (1.01-2.23)
Psychiatric comorbidity		
Substance use disorder	1.95 (1.11-3.44)	
Nonorganic psychosis		1.50 (0.60-3.79)
Anxiety disorder	1.50 (0.85-2.66)	1.25 (0.88-1.78)
Eating disorder	5.09 (1.07-24.33)	1.85 (1.11-3.09)
Personality disorder		2.29 (1.42-3.69)
Complicating social factors	1.67 (1.08-2.59)	1.55 (1.17-2.04)
Economy-related social problems	2.09 (1.18-3.69)	1.58 (1.08-2.32)
Social problems in the primary group		1.60 (1.15-2.24)
Violent behaviour	1.42 (0.81-2.47)	0.93 (0.59-1.48)

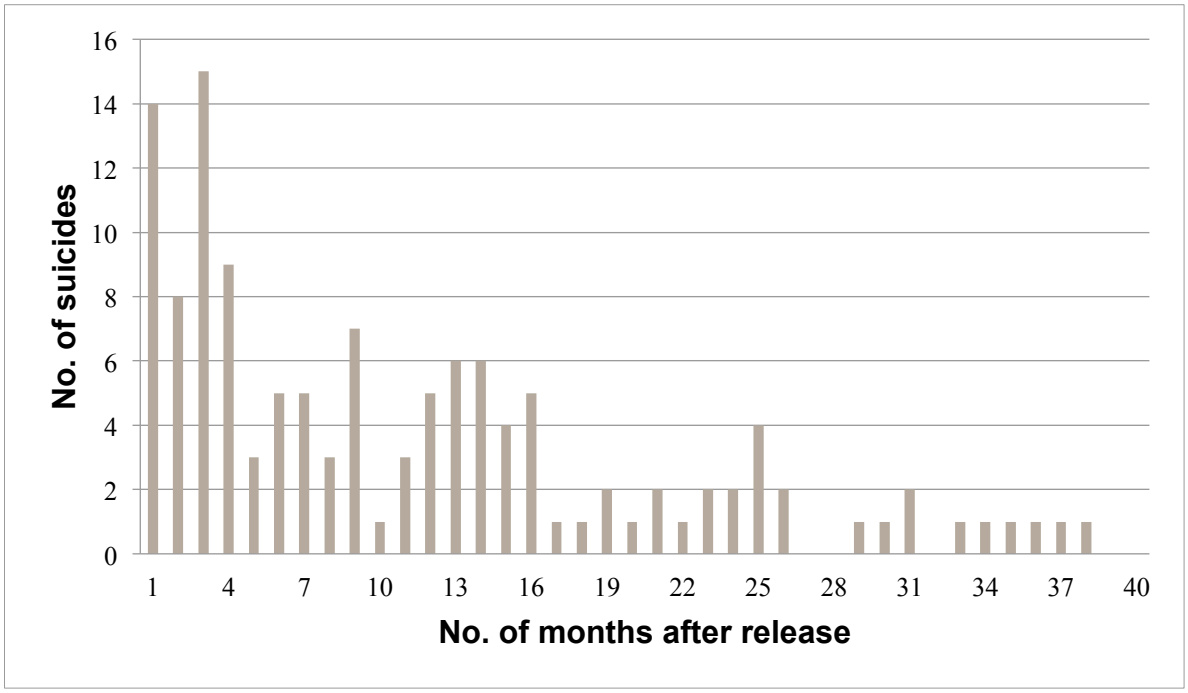
Women had higher adjusted odds for attempted suicide than men during follow-up (OR = 1.40, 95% CI =1.09-1.81). Most prominent risk factors for both genders were previous suicide attempt, affective episode and psychiatric inpatient care during the year before inclusion in the register.

4.2 STUDY II

4.2.1 Descriptive statistics

Between January 1, 2005 and December 31, 2009 we observed 26 985 prisoners being released 38 995 times. The proportion of women was small, only 7.6%. The mean age at release was 37.8 years. The median follow-up time was 1.2 years. A total number of 127 completed suicides were observed during the study period. Most of them occurred during the first 16 months (Figure 4.1). Naturally, the numbers of person years at risk were also falling for each month of the study period, making suicides rare towards the end of the follow-up period.

Figure 4.1. Number of suicides (N=127) among released prisoners in Sweden 2005–2009 by month after release, no suicides occurred later than 38 months after release in our study



The incidence rate was highest during the first 28 days after release with 12 suicides occurring, equalling 408 per 100 000 person years at risk (95% CI 211-712). The suicide incidence rate ratio was 58 compared with the control group, but with a 95% confidence

interval between 13 and 534. The incidence rate for suicide during the whole study period was 204 (170-243), equalling an incidence rate ratio of 18 (14-24).

4.2.2 Risk factors for suicide after release from prison

Psychiatric disorders were more common among the released prisoners than among the controls, with more than half (53.6%) having received a diagnosis at some point in life. Substance use disorder was the most prevalent diagnosis (47.0%). The released women had significantly higher prevalence than men in all studied diagnoses, except for psychotic disorder. Previous suicide attempts treated in a hospital were registered in 17.6% of the released prisoners.

The bivariate analysis of all explanatory variables in study II identified a few possible predictors associated with the studied outcome. We found no significant increase of risk by sex, age group, or in those with a history of violent crime. The significant variables were included in a multivariate Cox regression model.

Table 4.2. Multivariate Cox regression model, including non-overlapping predictors from the bivariate analysis, and hazard ratios presented with 95% confidence intervals

Explanatory variable*	Adjusted hazard ratio (95% CI)
Previous suicide attempt	2.5 (1.7-3.7)
Substance use disorder	2.1 (1.4-3.2)
Being born in Sweden compared with abroad	2.1 (1.2-3.6)

** Only the variables with significant results are shown.*

A history of affective disorder was less common and psychotic disorder, substance use disorder and previous suicide attempts were more common among released prisoners who committed suicide than among suicide victims in the control group (table 4.3). Almost 80% of the released prisoners who committed suicide had at some point experienced a psychiatric or substance use disorder.

The significant results for men and women combined were also significant for men only. Statistical power to analyse differences among the women was lacking, with only 12 suicides among released female prisoners and 3 suicides among the female controls. However, it was a strong statistical trend that substance use disorder was over-represented and affective disorder under-represented also among the released female prisoners (sex-divided data not shown in table 4.3).

Table 4.3. Characteristics of released prisoners that were also suicide deaths (N=127) and non-prisoner suicide controls matched on birth year and sex (N=102)

Explanatory variable	Released prisoner suicides % (n)	Control suicides % (n)
Born in Sweden	87.4 (111)	87.3 (89)
Psychotic disorder	16.5* (21)	7.8 (8)
Affective disorder	5.5# (7)	15.7 (16)
Substance use disorder	71.7* (91)	24.5 (25)
Personality disorder	9.5 (12)	7.8 (8)
Any psychiatric disorder (incl. substance use disorder)	78.7* (100)	42.2 (43)
Any psychiatric disorder (excl. substance use disorder)	7.1# (9)	17.6 (18)
Previous suicide attempt	41.7* (53)	24.5 (25)
All suicides	100 (127)	100 (102)

** Significantly higher than among the respective controls (Fisher's exact test, p<0.05)*
 # Significantly lower than among the respective controls (Fisher's exact test, p<0.05)

4.3 STUDY III

4.3.1 Descriptive statistics

In total, 665 self-harming patients were eligible for inclusion during the study period and 452 agreed to participate (68.0%). Participants who in the interview were found to have had no suicide intent at the self-harm act (NSSI) were excluded (n=83). Finally, 355 suicide attempters (133 men and 222 women) who had completed the Karolinska Interpersonal Violence Scale were included. Mean age was 40 years (range 18 to 92 years, median 35 years) and the women were significantly (p<0.001) younger with a mean age of 37 years, compared with the mean age of 45 years among the men. The gender difference with overrepresentation of women in the study population is only observed in the age groups 18-44 years.

In the total cohort of 355 suicide attempters 78 (22.0%) made repeated attempts within 6 months (28 men, 50 women) and of these, 5 were fatal (2 men, 3 women). Repeated attempts with violent method were recorded for 21 persons (5.9%). The mean total KIVS score was 6.0 with no significant gender difference (men 6.1, women 6.0, ANOVA p=0.771). While no gender differences were observed for the two childhood subscales, scores on both adulthood subscales differed significantly in men and women. Men scored higher on "expression of violence as an adult", and women on "exposure to violence as an adult".

4.3.2 Interpersonal violence and the risk of repeated suicide attempt

In bivariate logistic regression, having a KIVS total-score of 6 or above was associated with an increased risk for repeated suicide attempt within six months. The subscale "exposure to violence as an adult" was significantly associated with an increased risk for repeated suicide attempt within six months.

Table 4.4. Bivariate logistic regression generated odds ratios (OR) for one-step elevation in score on the KIVS in study II, with the outcome new suicide attempt within six months, results for men and women shown together

	OR	CI lower	CI upper	P-value
Expression of violence as a child	1.060	0.869	1.293	0.564
Expression of violence as an adult	1.045	0.851	1.284	0.675
Exposure to violence as a child	1.100	0.960	1.261	0.171
Exposure to violence as an adult	1.138	1.005	1.288	0.041*
KIVS total-score	1.052	0.995	1.113	0.074
KIVS total-score ≥6	1.809	1.083	3.024	0.024*

** Significant elevation of risk (p<0.05)*

The significant subscales in the logistic regression analysis were tested further using ROC curves. The dichotomous variable "KIVS total-score ≥6" generated a ROC curve with an AUC of 0.57 (p=0.049). A result of 6 or above on the KIVS was better than chance in predicting a repeated suicidal behaviour in 6 months (Table 4.5).

Table 4.5. Two-by-two table used to calculate predictive properties of the variable "KIVS total score ≥6" for predicting a repeated suicide attempt in 6 months, men and women analysed together

	Repeated suicidal behaviour in 6 months	No repeated suicidal behaviour in 6 months	Summation
KIVS≥6	48[a]	130[b]	a+b = 178
KIVS<6	30[c]	147[d]	c+d = 177
Summation	a+c = 78	b+d = 277	a+b+c+d = 355

Sensitivity = a/a+c = 61.5%
Specificity = d/b+d = 53.1%
Prevalence of outcome = (a+c)/(a+b+c+d) = 22.0%
Positive predictive value = a/(a+b) = 27.0%
Negative predictive value = d/(c+d) = 83.1%

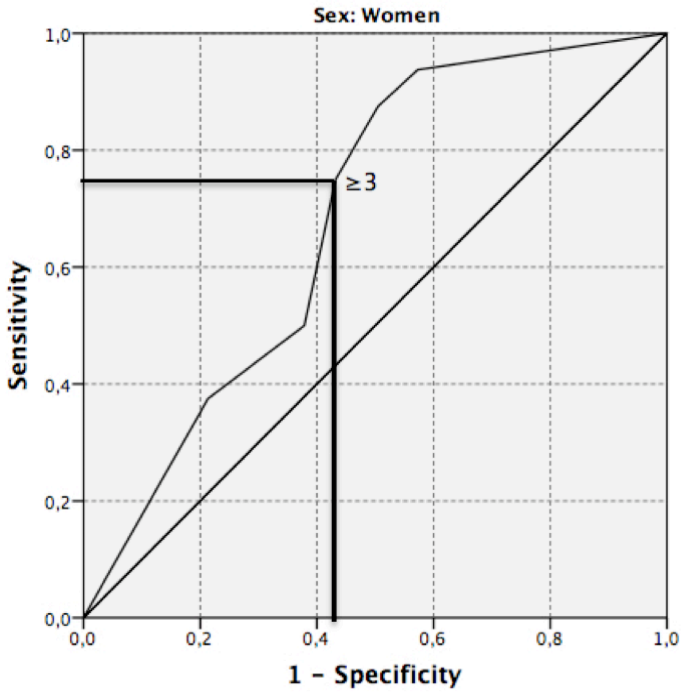
The subscale “Exposure to violence as an adult” could not significantly predict a new suicide attempt within six months when analysing its ROC curve (AUC=0.57, p=0.065).

A KIVS total-score ≥6 was associated with an increased risk for a new attempt using a violent method (OR=3.40, CI 1.22-9.49).

Neither the total score of KIVS nor any of the analysed subscales were significantly associated with repeated suicide attempt within six months in the gender-specific analysis. However, gender differences unfolded when analysing the outcome repeated attempt using violent method. In women, both the continuous variable KIVS total score (OR= 1.13, CI 1.01-1.26), and the dichotomous variable KIVS total score of 6 or above (OR=4.78, CI 1.32-17.3) were associated with elevated risk. Also, the subscale “exposure to violence as an adult” increased the risk of a new suicide attempt using a violent method within six months among women (OR=1.38, CI 1.05-1.81, p=0.020). No associations were observed in men.

The ROC curve for the dichotomous variable of KIVS total-score of 6 or above used as a test to predict women who repeated suicide attempt using violent method, showed an AUC=0.67 (p=0.025). Having a total-score of 6 and above thus predicted new suicide attempts using violent methods among women with a sensitivity of 81% and a specificity of 52%. Using the subscale “exposure to violence as an adult” as a test to predict repeated suicidal behaviour using a violent method within six months among women, generated a ROC curve (Figure 4.2) with an AUC of 0.68 (p=0.016) with an optimal cut-off point ≥3.

Figure 4.2. ROC curve for the KIVS subscale “Exposure to violence as an adult” and prediction of violent suicide attempt in women, the optimal cut-off point ≥3 is shown



With the use of the optimal cut-off score, it is possible to calculate the predictive properties of the subscale as shown in Table 4.6.

*Table 4.6. Two-by-two table used to calculate predictive properties of the variable "*Exposure to violence as an adult *≥3" for predicting a repeated suicide attempt with violent method among women within 6 months*

	Repeated violent suicidal behaviour in 6 months	No repeated violent suicidal behaviour in 6 months	Summation
KIVS≥6	12[a]	89[b]	a+b = 101
KIVS<6	4[c]	117[d]	c+d = 121
Summation	a+c = 16	b+d = 206	a+b+c+d = 222

Sensitivity = a/a+c = 12/16 = 75.0%
Specificity = d/b+d = 117/206 = 56.8%
Prevalence of outcome = (a+c)/(a+b+c+d) = 7.2%
Positive predictive value = a/(a+b) = 12/101 = 11.9%
Negative predictive value = d/(c+d) = 96.7%

5 DISCUSSION

5.1 DISCUSSION OF STUDY I

During a mean follow-up period of 2.4 years in study I, 351 (5.8%) bipolar patients engaged in suicidal behaviour of which thirteen were completed suicides. The strongest risk factors for suicidal behaviour were:

1) previous suicide attempt
2) an affective episode during the year before inclusion
3) to have had four or more depressive episodes in lifetime
4) to have received psychiatric inpatient care during the year before inclusion.

The point estimates of relative risk (OR's) ranges between 2 to 4 for these risk factors in both men and women.

The finding that previous suicide attempt is a strong risk factor for suicidal behaviour among bipolar patients is a confirmation of a well-studied fact[79,117,123,124,153]. However, the risk factors recent inpatient care and recent affective episode seem to be almost equally strong as predictors. The importance of the depressive features of the disorder reported in earlier research was thus confirmed in our study[117,154-156]. A need for inpatient care may indicate onset of an affective episode and more severe forms of the disorder. Altogether, the main findings of study I have implications for suicide prevention, since there are evidence-based treatments available that may prevent both recurrent affective episodes and subsequent need for hospitalisation of bipolar patients. In addition to medication[123], stable access to care and specialised programs for bipolar patients have shown positive effect in preventing suicide[126].

Economy-related social problems had low point estimates of risk elevation but were significant for both men and women. To our knowledge, this may be a novel finding. When examining previous research in his review, Hawton only found a non-significant correlation between unemployment and suicide attempts in bipolar patients[117]. However, it is complicated to assess economy-related problems in a uniform way, making comparisons between different research results hazardous.

There is inconsistency in the literature as to whether there is a difference in risk of suicidal behaviour between different subtypes of bipolar disorder. Some reviews have concluded that bipolar disorder type 2 is associated with a slightly higher risk[123,124,157], and two other reviews found no difference between subtypes[117,158]. In our study, no significant differences were found. One interpretation of our results is that other features of the disorder are of greater importance. For instance the intensity, severity and the numbers of depressive episodes[117], or the presence of atypical features[159], could be more relevant. However, future research of follow-ups of the same cohort using completed suicide as outcome may come to other conclusions.

Women had significantly higher odds for attempting suicide in this study. This is in contrast

with the review by Hawton[117] that reported no significant difference, but in line with an earlier review by Tondo[123] showing almost a doubling of risk for women. Hence, the results in this field are inconclusive, however, when evaluating the research on bipolar disorder and the risk for different suicidal behaviour, it is obvious that the gender paradox[160] observed in the general population in most countries, is less pronounced in bipolar patients. For instance, a large Swedish study of bipolar patients reported higher SMR's for completed suicide in women than in men[122].

Furthermore, some risk factors differed between men and women. Early onset of psychiatric problems, personality disorder and many lifetime mixed episodes were predictors for women, while comorbid substance use disorder was a predictor exclusively for men.

Substance use disorder doubled the risk of suicidal behaviour in bipolar men. This result is in contrast with a recent register study from Denmark that reported no significant contribution to risk of suicide when substance use disorder was added to bipolar disorder[77]. No gender specific analyses, lower resolution of data or a narrower outcome (only completed suicide) are differences in study design that may explain the different result in the Danish study.

The slightly different risk pattern between bipolar men and women in study I seems to be a novel finding indicating a need for further investigations of the gender differences.

5.2 DISCUSSION OF STUDY II

In study II almost 27 000 prisoners were released nearly 40 000 times over a follow-up time of up to five years. In this high-risk population 127 suicides were identified. The three main findings were:

1) the risk of suicide was 18 times higher among released prisoners compared to controls and the risk was even more pronounced during the first four weeks after release
2) the strongest risk factors were a) previous suicide attempt, b) substance use disorder and c) being born in Sweden
3) there was a different pattern in distribution of risk factors between victims of suicide among the released prisoners and the controls, with higher prevalence of diagnoses of substance use disorder and less of depression among the prisoners

The overall suicide rate is relatively high in an international comparison but still comparable with research from other parts of the world[130-133]. However, all previous studies have been conducted in countries with substantially higher prison population rates than Sweden. The consequence of a low prison population rate is that the average prisoner tends to be more deeply involved with crime and associated problems. Furthermore, the transition to life outside prison is known to be associated with increased risk of homelessness, unemployment, and relapse in abuse of alcohol and illegal substances[161,162]. Also, in our study we used non-

convicted controls to contrast with the released prisoners. These circumstances may explain the relatively high suicide rates reported in study II.

Previous suicide attempt was a strong risk factor for suicide in released prisoners. This confirms the often replicated finding that previous suicidal behaviour is the strongest predictor of suicidal behaviour[23]. However, substance use disorder was an almost equally strong predictor in our study. Substance use disorder has previously been linked with increased risk of suicide in the general population[23,163], in suicide attempters[79,84] and also in prisoners[164]. No other psychiatric diagnoses had a significant effect on risk in this study. This is probably a type II error. Nevertheless, the findings in study II altogether suggest that substance use disorder plays an especially important role as a marker of suicide risk in released prisoners. Perhaps the substance use disorder masks other conditions in this clientele, preventing other psychiatric disorders from being properly identified.

The predominantly male ex-prisoners in study II and the bipolar men in study I share substance use disorder as a risk factor for suicidal behaviour. Mortality from suicide has been reported to dominate among male opioid addicts[165,166]. Heroin use, injection drug use and a history of overdose were factors associated with increased mortality among Swedish substance using ex-prisoners in a recent follow-up study[167]. There are several evidence-based treatments for different kinds of substance use disorders, and one recent study from Australia reported promising results in reducing mortality from unnatural causes in prisoners with opioid substitution therapy while in prison[168]. There are no similar studies on released prisoners. However, it is highly plausible that effective treatment of substance use disorders may reduce risk for both suicide and other unnatural deaths after release from prison.

Being born in Sweden compared with abroad was linked to a higher risk of suicide among released prisoners in study II. This is in line with previous findings for both sexes in a cohort study covering the Swedish population in which being born in Sweden was compared with being born in a non-Nordic country[57]. Also in tune with our result, a study from Denmark has shown a decreased risk of suicide attempts and increased risk of violent offending in first generation male immigrants with low socioeconomic status compared with native Danes[169]. In yet another Swedish population study, young female immigrants but not young male immigrants had an increased risk of suicide attempts[170]. Consistently, the suicide rate among first generation immigrants tends to reflect the suicide rate in the country of birth[171]. A national Swedish report[172] from 2005 showed that over 60% of the immigrants who were suspected of crime between 1997 and 2001 were from outside the European Union. However, in study II we lacked more detailed data on specific birth countries. Hence, further analysis on this issue was beyond our scope.

Our hypothesis that violent crime would be associated with higher risk of suicide than non-violent crime, did not prevail. Several earlier studies have reported a link[131,173-175]. However, our result is in line with a population study based on Danish population registers where psychiatric and social risk factors were accounted for[176].

In the comparison of prevalence rates of psychiatric variables between suicide victims among the release prisoners and the controls, two things were notable. Firstly, the prevalence of substance use disorder is significantly higher in the released prisoners, with 71.7% having received a diagnosis at some point. Secondly, the prevalence of affective disorder is strikingly low among the released prisoner suicides with only 5.5% ever having received this diagnosis compared with 15.7% among controls. These findings suggest that suicide among released prisoners is more related to substance use disorders and less related to affective disorder than is suicide in the general population. The differences may however be explained in different ways. Personality traits in the form of impulsive aggressiveness may predispose for both criminal and suicidal behaviour, as well as substance use disorders[46]. This theory also implies that the pathway to suicide in released prisoners perhaps does not involve affective disorders to any large extent. Another explanation can be that the affective symptoms in released prisoners are masked by the substance use disorder or that the prisoners have a different health-care seeking behaviour, making them less prone to be hospitalised for affective disorders. However, almost 80% of the suicide victims among the released prisoners had at least one psychiatric or substance use disorder diagnosis, indicating that they to a higher extent than the controls who committed suicide, have been in contact with the health care system.

5.3 DISCUSSION OF STUDY III

In study III we found that interpersonal violence measured with the KIVS to some extent could enhance the prediction of a repeated suicide attempt within the first six months after a suicide attempt. To our knowledge this is the first study to link a certain degree of reported interpersonal violence with repetition of suicidal behaviour. The finding is relevant from a suicide prevention perspective since repetition of suicide attempts in itself has been found to elevate the risk for eventual suicide[177], especially among young patients[178].

Reported experiences of interpersonal violence were common among the suicide attempters. The mean total KIVS score of 6.0 is similar with the mean score reported in another Swedish cohort of suicide attempters[139]. The latter study also included a healthy control group with a mean total score of 2.9 on the KIVS, showing that suicide attempters report experiences of interpersonal violence to a larger extent than the general population.

In contrast with the earlier study by Jokinen and co-workers[139], when analysing the separate subscales of the KIVS, we found that being a victim to violence as an adult was associated with repeated suicidal behaviour but not the subscales covering exposure to violence as a child and expression of violence as an adult. The disparity in results between the studies is probably due to differences in study design. In our study a different outcome was studied (including both nonfatal and fatal attempts) and a much shorter follow-up time was used. Also, our study had a larger study population. The results from our study and the previous study on the KIVS indicate that different experiences of interpersonal violence may affect

subsequent risk for attempted suicide and completed suicide differently. It is also possible that being a perpetrator or a victim of violence, affect short-term and long-term risk differently.

The finding that being a victim of violence as an adult could predict violent suicide attempts among female suicide attempters harmonise with other research showing that domestic violence against both men and women is associated with suicide attempts[179,180]. For men we could not find this association. The reason for this could be lack of statistical power since the number of men with violent repeated attempts was limited. Violent methods are associated with higher immediate lethality[152] but also with elevated risk of later suicide[150], probably because it indicates a stronger suicidal intention. In large epidemiological studies of suicide attempters, women tend to choose violent methods more seldom than men[150], in contrast with our present result. An important methodological difference that may partly explain this is that we in our clinical sample excluded self-harmers without suicide intent, something that cannot be performed in larger epidemiological studies based on data relying on ICD-10 codes that does not differentiate between non-suicidal self-harm and suicide attempt. This is a relevant distinction since the choice of method in a self-harm act most likely is linked with the intention of the act. Another possible reason for the observed gender difference is that interpersonal violence experienced by women may have a slightly different impact on their suicidal behaviour than it has in men, perhaps making them more likely to use violent methods. However, before any causal patterns of this sort can be outlined we need more studies that can replicate our finding and further unravel the nature of the observed associations in this study.

A recent Swedish population study showed a link between depression and violent crime[181]. The authors conclude that assessment of risk of violence, which to a large extent depends on information about previous experiences of interpersonal violence, should be considered routinely for certain subgroups of patients with depression, including those who have engaged in self-harm. The results from our present study support a similar notion that questions about interpersonal violence could also be relevant from a suicide risk assessment perspective, and for this reason should be used more often in certain clinical situations, such as in the aftermath of a suicide attempt. However, despite the significant association with repeated suicide attempt, the KIVS provides limited sensitivity and specificity in predicting new suicide attempts on its own, and should only be considered as a complement to regular risk assessment tools. A recent paper found no correlation between scores on the Suicide Intent Scale and the KIVS suggesting that the scales measure different properties, making the scales appropriate to combine[140]. However, further research is needed to disentangle the associations and causal pathways between interpersonal violence and suicidal behaviour, to enable better prediction and tailor-made preventive interventions.

5.4 GENERAL DISCUSSION

What happens if someone belongs to all three high-risk populations described in this thesis? It is not correct to multiply risk rates from different studies. However, a recent study by Webb and co-workers[148] somewhat synthesise the findings of the three studies included in this thesis. They reported that 22% of the bipolar patients in a Swedish population-based register sample had engaged in either criminal or suicidal behaviour. The risk of completed suicide in this combined high-risk group was 19 times elevated. Risk factors were previous suicide attempts, substance use disorders and that the two first affective episodes required admission to a hospital. The risk of committing violent crime in this group was 5-fold. A violent crime usually involves interpersonal violence. Hence, these findings bind together the results of the three studies included in this thesis, suggesting that these risk factors are independent yet often coexisting, and of special importance in the assessment of suicide risk in specific groups of patients.

5.5 STRENGTHS AND LIMITATIONS

5.5.1 Study I

The primary strength of study I is the large sample size with highly valid patient data obtained from natural clinical settings. This allowed us to stratify on gender and to include many explanatory variables in the same model, without losing too much of statistical power. Yet, the amount of suicides occurring was too small for specific analysis, and when comparing the result in study I with other cohorts of bipolar patients, the proportion that have engaged in suicidal behaviour may seem low. One important reason is probably that our cohort includes many patients without any history of inpatient care. A fairly large part of bipolar patients in contact with an outpatient clinic are in a stable condition for long periods of time. Other previous studies often only included bipolar patients who either just made a suicide attempt or were hospitalised, favouring more severe forms of the disorder.

A weakness in study I is the participation rate of 50%. There is no data available for the bipolar patients who do not participate in BipoläR. Hence, some inclusion bias cannot be ruled out. Furthermore, there are a few potentially relevant factors that are lacking in BipoläR. For instance, a more detailed measurement of the severity of the disorder, and details about the suicidal behaviours reported in the register, would have been relevant clinical information to analyse.

5.5.2 Study II

The strengths of study II are the common strengths of population-based register studies. The Swedish national registers are the largest in the world with complete coverage and prospectively collected data. The validity of the Swedish Patient Register has been evaluated

for schizophrenia and bipolar disorder and was found to be of high quality[143,182]. The large size of the cohort gave us statistical power to study the rather unusual outcome suicide. Unlike in earlier studies of suicide in released prisoners we were able to analyse how psychiatric disorders affected suicide risk and how the pattern of risk factors differed from the general population. However, the high suicide rate ratios in the study need to be interpreted with some caution due to the large confidence intervals.

Another limitation of study II stems from fact that the Swedish Patient Register did not cover outpatient data before 2001 and since then only includes diagnoses from specialised outpatient care. People with psychiatric problems who were treated exclusively in primary care or who never came in contact at all with the health care system were not included.

5.5.3 Study III

In study III we used the largest clinical cohort yet to analyse results on the KIVS and the association with suicidal behaviour. We were able to exclude patients with NSSI in this study making the studied group less heterogeneous. The large sample size enabled gender specific analyses to be performed. However, the completed suicide cases were too few to be analysed separately in this cohort. With more patients included, and using a longer follow-up period, we may be able to analyse completed suicide as only outcome in the future.

In study III we rely on self-reported information about interpersonal violence. There is risk of recall bias when asking sensitive questions shortly after a traumatic event such as a suicide attempt. While this does not affect the internal validity of our results, it limits the generalisation to other patient groups. Furthermore, since information about the studied outcome was extracted from the patients' electronic medical records, suicide attempts that were not mentioned there are lacking. This introduces a bias that probably favours more severe forms of suicidal behaviour with higher probability of being reported in medical records. This is important to remember when interpreting our results.

5.6 CLINICAL IMPLICATIONS FOR SUICIDE PREVENTION

The studies in this thesis have analysed possible risk factors for suicide within different high-risk populations. Knowledge about risk factors is essential when conducting a suicide risk assessment in ordinary clinical work.

Table 5.1. A summary of the clinical implications for suicide prevention

Study I – Bipolar patients
• Bipolar patients constitute a high risk population for suicidal behaviour. Hence, identification of the diagnosis is important and has implications for the assessment of risk for suicide. • Several aspects of the bipolar disorder are important to differentiate the risk for suicide within this high risk population. Details about the course and difficulty level of the bipolar disorder are essential. • Gender specific factors may be important to take into consideration when making suicide risk assessments in bipolar patients.
Study II – Released prisoners
• Risk of suicide is sharply elevated shortly after release from prison. This is important knowledge for all health care and social workers that come in contact with released prisoners. • Information about previous suicidal behaviour is vital for a proper assessment of risk in this population. Therefore, forwarding of this information in the care chain between prison and probation services, health care and social services is important. • Within this high risk population, substance use disorders seem to be of special relevance for the risk of suicide. Today, several evidence-based treatments exist and should be made available for prisoners in connection with release to diminish risk of suicide.
Study III – Suicide attempters
• Experiences of interpersonal violence is associated with elevated risk of repeated suicidal behaviour among suicide attempters. This suggests that questions about interpersonal violence could be relevant in clinical suicide risk assessments after suicide attempts. • Female suicide attempters who were victims of violence in adulthood used more violent methods when attempting suicide. This implies that questions about victimisation could be important also from a suicide risk assessment perspective.

6 CONCLUSIONS

The act of killing oneself is the result of a process unique for each individual. There are, however, patterns in thoughts, behaviours and circumstances surrounding every suicide, which may be possible to distinguish in more or less well-defined populations. Better knowledge about high-risk groups can contribute to the prevention of suicides.

In the three papers included in this thesis factors related to suicidal behaviour have been studied. With the use of three different sources of data, we have been able to address questions about risk factors for suicide within three different high-risk groups. Our findings support the notion that the magnitude of various risk factors may differ between groups of patients, motivating further research in specific high-risk populations. When managing suicide risk in bipolar patients the clinician needs to pay close attention to the specific character and development of the disorder. In prisoners, there are vulnerable time periods, with the time after release being a high-risk situation, especially if there is a history of substance use disorder. When assessing risk after a suicide attempt, information about experiences of interpersonal violence may complement the clinical picture and help the prediction of repeated suicidal behaviour and possibly indicate a tendency to choose more violent and lethal methods.

Even though prediction of suicide is difficult, more detailed knowledge about high-risk groups and specific risk factors may contribute to the understanding of suicide and to the improvement of suicide prevention. Identification of high-risk groups can influence how resources are allocated in society. For instance, the results of study II have partly formed the basis for a bill in the Swedish parliament in September 2015[183].

7 FUTURE STUDIES

Research on suicide needs to take into account the heterogeneity of conditions, psychological mechanisms, situations and behaviours that can lead to suicide. As the results of this thesis have indicated, factors of importance for assessing risk can vary in different populations. Studies with large samples, which make it possible to investigate risk in subgroups, are very important.

The use of psychiatric quality registers in research is a promising new way to study factors related to suicidal behaviour in different diagnostic domains. For instance, there are quality registers in Sweden for eating disorders (RIKSÄT), ADHD (BUSA) and psychotic disorders (PsykosR) that could be used in a similar way as in study I to identify specific risk factors for suicidal behaviour. BipoläR has already been used for other research projects. For instance, gender differences in the treatment of bipolar disorder in Sweden have been studied by Karanti and co-workers[184]. Data from BipoläR has also been included in an international research project in collaboration between KI, NIMH and the Stanley Center for Research in the so-called STANLEY Study. So far, this project has generated several papers on genetic and environmental causes of bipolar disorder[185-187]. In the future, with both more included patients and longer follow-up periods in BipoläR, it will be possible to study risk factors associated with completed suicide. It may also be possible to observe how given treatment and occurrence of suicidal behaviour co-vary.

The high suicide rates among released prisoners in study II motivate further research in this high-risk group. That could include studies on the effect of imprisonment itself, the importance of psychosocial factors, and the effect of treatment after release. Epidemiological studies using population-based register data as in study II can also be used to identify further high-risk populations for suicide. Swedish registers are the largest and most complete population registers in the world. The relationship between criminality and suicidal behaviour can be further studied in several ways using cross-linkage of registers. For instance, people convicted for crimes but with other penalties than prison, are sparsely studied with regard to suicidal behaviour. The subscription register has been used to study how different medications affects criminal behaviour[188,189]. The naturalistic study design is associated with obvious limitations, but similar studies with suicidal behaviour as the studied outcome, and exposure to different medications, could possibly generate relevant insights for suicide prevention.

There is a need for large clinical studies of suicide attempters. Despite a great number of developed scales and tools for structured suicide risk assessments, none has been found to have acceptable predictive properties to motivate more widespread use[106]. However, continued research on risk factors possibly associated with suicidal behaviours, can still play an important role in the development of risk assessments made by clinicians. Evaluations of interventions are also necessary to develop and enhance preventive efforts directed at this high-risk group. Finally, the association between interpersonal violence and suicidal behaviour needs to be studied further. A larger clinical sample and a longer follow-up period may enable analyses with completed suicide as studied outcome in the future.

8 SVENSK SAMMANFATTNING

8.1 BAKGRUND

Ämnet för avhandlingen är riskfaktorer för suicid och suicidförsök i tre olika högriskgrupper; bipolära patienter, frigivna fångar och personer som överlevt suicidförsök. I delstudie I undersöker vi faktorer relaterade till bipolära tillstånd och risken för suicidförsök. Frigivna fångar har höga suicidtal jämfört med den allmänna befolkningen men lite är känt om specifika riskfaktorer. Delstudie II undersöker vilken roll psykiatriska riskfaktorer har i denna population. I delstudie III undersöks huruvida information om interpersonellt våld kan bidra till bedömningen av risk för upprepat suicidförsök bland personer som överlevt ett suicidförsök.

8.2 SYFTEN

Det övergripande målet med avhandlingen är att bidra med fördjupade kunskaper om riskfaktorer inom tre högriskgrupper för suicid. Detta kan ge förbättrade möjligheter att identifiera personer som löper särskilt hög risk för suicid så att förebyggande insatser kan fördelas med bättre precision.

8.3 METODER

Alla tre delstudier är utformade som kohortstudier där riskfaktorer för suicidalt beteende analyseras inom en högriskgrupp.

Studie I

Delstudie I bygger på 6 068 bipolära patienter som inkluderats i kvalitetsregistret BipoläR och följts åren 2004-2012. Utfallet i denna studie är suicidförsök och de riskfaktorer som studeras inkluderar olika karaktäristika av de bipolära tillstånden, samsjuklighet samt sociala förhållanden.

Studie II

Delstudie II baseras på 26 985 fångar som släpptes 38 995 gånger under åren 2005-2009. Data är hämtad ur databasen CRIME II, upprättad på MEB, KI, som inkluderar uppgifter ur bland annat Kriminalvårdens klientregister och Socialstyrelsens patientregister och dödsorsaksregister. Det studerade utfallet är fullbordat suicid och psykiatriska riskfaktorer analyseras. Som jämförelsegrupp valdes icke-dömda köns- och åldersmatchade kontroller ur allmänbefolkningen i relationen 1:10.

Studie III

Delstudie III består av data insamlade i en multicenterstudie där 355 personer som överlevt ett suicidförsök genomgått en strukturerad intervju där KIVS ingått. KIVS och dess delskalors möjligheter att förutse upprepat suicidförsök inom ett halvår analyseras.

8.4 RESULTAT

Studie I

De viktigaste riskfaktorerna för suicidförsök under uppföljningen av de bipolära patienterna i delstudie I var nyligen genomgången affektiv episod, tidigare självmordsförsök och att nyligen vårdats inom psykiatrisk slutenvård. För män innebar samtidigt substansmissbruk en signifikant riskökning medan samtidig personlighetsstörning utgjorde en riskfaktor för kvinnorna.

Studie II

I delstudie II identifierades 127 fullbordade suicid bland de frigivna fångarna under uppföljningstiden. Det motsvarar en 18-faldig incidensökning jämfört med kontrollgruppen. Viktigaste riskfaktorerna för suicid var tidigare suicidförsök, tidigare substansmissbruk samt att vara inrikes född.

Studie III

Av de 355 studiedeltagarna i delstudie III upprepade 78 personer ett suicidförsök inom sex månader. En totalsumma på 6 och mer på KIVS innebar en ökad risk för upprepat suicidförsök och predicerade nytt försök med en sensitivitet på 62% och en specificitet på 53%.

8.5 SLUTSATSER

De viktigaste kliniska slutsatserna är att 1) en kliniker bör vara uppmärksam på risken för suicidala handlingar hos bipolära patienter som uppvisar depressiva drag och som har svårare och mer instabila former av sjukdomen, 2) frigivna fångar har en kraftigt förhöjd suicidrisk den första tiden i frihet och information om tidigare suicidförsök och missbruksproblematik är särskilt viktig för bedömningen av risk i denna patientgrupp, och 3) information om interpersonellt våld kan bidra vid bedömningen av risk för upprepad suicidhandling inom ett halvår efter ett suicidförsök.

Fynden i de tre delstudierna i avhandlingen belyser vikten av att studera olika riskfaktorers betydelse i olika sammanhang och i olika grupper av patienter.

9 ACKNOWLEDGMENTS

I would like to express my heartfelt gratitude to all people who have helped and encouraged me during the work with my thesis. Particularly I would like to thank the following:

Bo Runeson, my main supervisor, for his wisdom. Your ability to find solutions and to always be able to make improvements is admirable. I've never left a meeting with you without a positive spirit and a clear direction forward. I am eternally grateful for all that you have done for me.

Jussi Jokinen, my co-supervisor, for his helpfulness, quick responses and constant support. It has always been very smooth and easy to work together.

Kaj Forslund, my mentor, who early on was a great inspiration for me in my clinical work. I will never forget how you helped me out with a very difficult risk assessment in the middle of the night at the Karolinska Hospital in 2001.

My research room mates over the years, **Henrik Lysell** and **Karin Beckman** at St. Göran's hospital. You have no idea how much I appreciate you.

Dag Tidemalm, who helped me out a lot in the beginning. I wish I were more like you as a researcher. You are a role model.

Marie Eriksson Dahlin, for all helpful input and fun discussions over the years.

Åsa Lindh, for being a supportive research colleague and for encouraging me to take the necessary steps to finally solve the Endnote problem.

Ingela Kärkkäinen Malmsjö, for all help along the way and for final improvement of the layout of the thesis.

Seena Fazel, for being a very encouraging co-author and research colleague.

All other co-authors of the papers included in this thesis, you have all been a pleasure to work with.

The Research school for clinicians in psychiatry at the Karolinska Institutet, for an excellent research education.

William Basinski, the avant-garde composers of the Disintegration tapes, a musical piece that I have listened to on repeat while writing this thesis.

Also, the funding agencies for this thesis are gratefully acknowledged: Centre for Psychiatry Research (CPF), Stockholm County Council, Bror Gadelius stiftelse, Kriminalvårdens FOU and Lennart Wetterbergs forskningsstiftelse.

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